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Articles

Hormonal Changes and Catabolic/Anabolic Imbalance in Chronic Heart Failure and Their Importance for Cardiac Cachexia

Stefan D. Anker, MD; Tuan Peng Chua, MD;
Piotr Ponikowski, MD; Derek Harrington, MRCP; Jon W. Swan, MD;
Wolfgang J. Kox, MD, PhD; Philip A. Poole-Wilson, MD; ; Andrew J. S. Coats, DM

From Cardiac Medicine, National Heart and Lung Institute, Imperial College School of Medicine, London, UK (S.D.A., T.P.C., P.P., D.H., J.W.S., P.A.P.-W., A.J.S.C.); the Department of Internal Medicine III/Cardiology, Martin-Luther-University Halle-Wittenberg, Halle/Saale, Germany (S.D.A.); and the Department of Anesthesiology and Intensive Care Medicine, University Hospital Charité, Humboldt University Berlin, Germany (W.J.K.).

Abstract

Background The role of hormonal and cytokine abnormalities in the development of cardiac cachexia remains obscure.

Methods and Results Healthy control subjects (n=16) and patients with chronic heart failure (CHF), classified clinically as cachectic (8% to 35% weight loss over ≥6 months before study, n=16) or noncachectic (n=37), were assessed for markers of disease severity (maximal oxygen consumption, left ventricular ejection fraction, NYHA functional class). These markers were compared with plasma concentrations of potentially important anabolic and catabolic factors. The degree of neurohormonal activation and catabolic/anabolic imbalance was closely related to wasting but not to conventional measures of the severity of heart failure. Compared with control subjects and noncachectic patients, cachectic patients had reduced plasma sodium and increased norepinephrine, epinephrine (all $P<.0001$), cortisol, tumor necrosis factor (TNF)-α (both $P<.002$), and human growth hormone ($P<.05$). Insulin-like growth factor-1,

testosterone, and estrogen were similar in all groups. Insulin was increased only in the noncachectic patients ($P<.005$ versus control subjects). Dehydroepiandrosterone was reduced in the cachectic patients ($P<.02$ versus control subjects). Insulin, cortisol, TNF-α, and norepinephrine correlated independently with wasting in CHF ($P<.05$; multiple regression of these four factors versus percent ideal weight, $R^2=.50$, $P<.0001$).

Conclusions Cachexia is more closely associated with hormonal changes in CHF than conventional measures of the severity of CHF. This study suggests that the syndrome of heart failure progresses to cardiac cachexia if the normal metabolic balance between catabolism and anabolism is altered.

Key Words: heart failure • hormones • metabolism • catecholamines • cachexia

Introduction

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Chronic heart failure is a heterogeneous syndrome with an overall adverse prognosis. Two particular predictors of adverse prognosis are neurohormonal abnormalities[1] and the development of cachexia.[2]

The syndrome of cardiac cachexia has been recognized for many centuries,[3] but little is known about the mechanisms of the transition from heart failure to cardiac cachexia. Even the definition of cachexia and the characteristics of the cachectic patient are controversial. More than 30 years ago, the pathogenesis of cardiac cachexia was linked to dietary and metabolic factors.[4] In 1990, Levine et al[5] and subsequently others[6 7] showed that TNF-α in plasma is increased in patients with severe heart failure and coexisting cardiac cachexia, as in other wasting disorders. The plasma concentrations of TNF-α partly reflect the local tissue concentration, which is more closely related to muscle wasting.[8] Cytokine activation is a potential causal mechanism for the development of cachexia.

Cardiac cachectic patients suffer from loss of both muscle (ie, protein reserves) and fat tissue (ie, energy reserves), indicative of increased catabolism. An increased resting metabolic rate, regulated primarily by thyroid hormones[9] and catecholamines,[10] has been reported in CHF patients.[11] Cortisol, another catabolic hormone, is also increased in untreated severe congested heart failure patients.[12] Less is known about anabolic metabolism in heart failure. Anand et al[12] found hGH to be greatly increased (≈10-fold) in untreated patients with severe heart failure. To date, these results have not been confirmed by others. Increased plasma insulin levels and insulin resistance occur in patients with CHF.[13]

The neurohormonal hypothesis[1] postulates that heart failure progresses because activated endogenous neurohormonal systems exert a deleterious effect on the heart and circulation. Several studies have found neurohormonal activation to be strongly related to mortality,[14 15 16]

but different hormones correlate only weakly with each other.[15] Norepinephrine and plasma renin activity were found not to be related to peak oxygen consumption (peak $\dot{V}O_2$) or LVEF.[16] Left ventricular function, exercise capacity, clinical status, and sympathetic activation were independently related to the progression of CHF.[16]

No previous study has assessed the spectrum of catabolic and anabolic abnormalities in patients with CHF with different degrees of body wasting. We undertook the present study to compare the hormonal changes linked to catabolism and anabolism that occur in the presence and absence of cachexia in patients with CHF. We sought to determine whether neurohormonal changes in CHF were more closely related to the onset of cachexia than to other conventional markers of the severity of heart failure.

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Patient Population and Characteristics

Measurements were made in 53 male patients with mild to severe CHF and 16 male healthy control subjects of similar age (range, 46 to 68 years). The diagnosis of CHF was based on a history of congestive heart failure of at least 6 months (range, 1 to 20 years) with symptoms, reduced exercise tolerance, cardiomegaly, and objective left ventricular functional impairment. At the time of investigation, all CHF patients were clinically stable. The patients had no clinical signs of acute infection or other primary cachectic states (such as cancer, thyroid disease, or severe liver disease), had no residual signs of peripheral or pulmonary edema, and were studied when free of ascites. No patient was limited by exertional angina. Patients with chronic lung disease, hemodynamically important valve disease, neuromuscular disorders, myocardial infarction within the previous 12 weeks, renal failure, peripheral vascular disease, or excessive alcohol intake were excluded.

Thirty-seven CHF patients were not cachectic (age range, 49 to 75 years). Sixteen CHF patients (age range, 40 to 77 years, P=.08 versus noncachectic patients) had signs of clinical cardiac cachexia. Cardiac cachexia was defined clinically as documented nonintentional dry weight loss of ≥5 kg (all >7.5% of their previous normal weight) over a period of at least 6 months. To exclude patients with intentional weight loss, a second criterion of a body mass index (weight/height^2) of <24 kg/m^2 was used. All cachectic patients also complained of their weight loss. The weight loss amounted to 6 to 30 kg (mean, 11.8±1.5 kg, or 8% to 36% loss of previous body weight) in the preceding 0.75 to 11 years (ie, 6.0±0.9 kg/y).

All subjects performed a maximal treadmill exercise test (modified Bruce protocol, Amis 2000[17]) for estimation of peak $\dot{V}O_2$ (in mL·kg^{-1}·min^{-1}). In patients, the LVEF was measured with radionuclide ventriculography. The protocol was approved by the Ethics Committee of the Royal Brompton Hospital, London. All patients gave written informed consent before the study.

Hormonal Measurements

Blood samples were collected in the morning, between 9 and 10 AM, after a fasting period of ≥12 hours. An antecubital polyethylene catheter was inserted, and after supine rest for at least 20 minutes, 25 mL of venous blood was drawn. After immediate centrifugation, aliquots were stored at -70°C until analysis. IGF-1 (Medgenix; sensitivity, 0.25 ng/mL), hGH (Nichols Institute Diagnostics; sensitivity, 0.02 ng/mL), thyroid stimulating hormone (Bering Diagnostics; sensitivity, 0.3 mU/L), reverse T_3 (Biodata; sensitivity, 0.014 nmol/L), PRA (Biodata SPA; sensitivity, 0.039 $ng \cdot mL^{-1} \cdot h^{-1}$), and aldosterone (DPC; sensitivity, 16 pg/mL) were measured by radioimmunoassay. Epinephrine and norepinephrine were measured with high-performance liquid chromatography (sensitivity, 0.1 ng/mL for both). TNF-α was measured with an ELISA with a lower limit of detectability of 3.0 pg/mL (Medgenix). This test uses three antibodies directed against distinct epitopes of TNF-α and is not influenced by soluble TNF receptors,[18] ie, it measures the total TNF concentration, bound or unbound. All other parameters (including steroid hormones and insulin) were analyzed by routine analysis in our hospital.

Statistical Analysis

All results are presented as mean±SEM. When ANOVA showed significant differences, Fisher's post hoc test was applied. To analyze relationships between variables, simple linear regression (least-squares method), multivariate analysis, and stepwise regressions were performed (StatView 4.5, Abacus Concepts Inc). To take account of multiple analyses, a probability value of <.01 was considered statistically significant. For multiple and stepwise regression analysis, a value of $P<.05$ was used to indicate statistical significance. If blood results were below the limit of detectability of a test, the lower limit of detection was recorded. Log-transformed values were used for statistical analysis of basal insulin levels.

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Clinical Details

The clinical details and results of the treadmill exercise tests of the patients and control subjects are shown in Tables 1 and 2. The age, body mass index, and percent ideal weight[19] of the 53 patients with CHF were similar to those of the 16 control subjects. The healthy control subjects had a significantly higher treadmill exercise time and exercise capacity. The cachectic and noncachectic patients with CHF had similar peak $\dot{V}O_2$, LVEF, NYHA functional class, disease pathogenesis, drug medication, mean furosemide equivalent dose (106±18 mg versus and 103±19 mg), and duration since onset of heart failure (both patient groups: mean, 5±1 years; median, 3 years) but differed significantly in weight, body mass index, and percent ideal weight (Table 1). Patients with cardiac cachexia (44.9±0.9 g/L) had similar and normal albumin levels compared with control subjects (45.1±0.6 g/L) and noncachectic CHF patients (43.2±0.4 g/L, $P<.05$ for noncachectic CHF versus control and cachectic subjects). Total protein levels were highest in cachectic CHF patients (72.1±0.9 g/L) compared with noncachectic (69.2±0.7 g/L, $P<.05$ versus cachectic) and control subjects

(66.9±0.7, *P*=.0004 versus cachectic, *P*=.053 versus noncachectic subjects). Mean bilirubin levels (ANOVA *P*=.18) and aspartate aminotransferase activity (ANOVA *P*=.07, trend for higher levels in noncachectic CHF) did not differ significantly between groups.

View this table: [in this window] [in a new window] **Table 1.** Characteristics of cCHF and ncCHF Patients Compared With Healthy Control Subjects

View this table: [in this window] [in a new window] **Table 2.** Characteristics of 16 Cachectic and 37 Noncachectic CHF Patients

Hormonal Determinations

All CHF patients. Compared with control subjects, the total group of CHF patients had increased creatinine, PRA, reverse T_3, basal insulin levels, and lowered plasma sodium (all *P*<.005, Table 3 ⊡). In addition, trends for increased norepinephrine, epinephrine, and aldosterone as well as for reduced DHEA (*P*=.01 to .06) were found.

View this table: [in this window] [in a new window] **Table 3.** Results of Hormone Analysis in Healthy Control Subjects and Patients With CHF: Heart Failure Patients Subgrouped by Cachectic State

Cachectic patients. The results for cachectic and noncachectic CHF patients are shown in Table 3 ⊡. The plasma sodium concentration was decreased, and epinephrine, norepinephrine, cortisol, and TNF-α were substantially increased in cachectic CHF patients (all *P*≤.0002 versus noncachectic CHF patients, all *P*≤.0015 versus control subjects). In cachectic patients, aldosterone and hGH were increased compared with noncachectic patients (both *P*<.01), and aldosterone, PRA, reverse T_3, and creatinine were increased compared with control subjects (all *P*<.005). Individual values varied from normal to greatly elevated levels in the cachectic patients. There were trends for increased hGH and reduced DHEA in cachectic patients compared with control subjects (both .01<*P*<.05). This trend reached statistical significance for DHEA, when the cachectic patients with <85% of normal weight (n=9; mean, 6.4±1.5 nmol/L) were compared with the control subjects (*P*=.008).

Noncachectic patients. Compared with control subjects, the noncachectic patients had significantly increased insulin (*P*<.005) and trends toward increased creatinine, reverse T_3, and PRA (all .01<*P*<.05). The noncachectic patients had levels of epinephrine, norepinephrine, TNF-α, cortisol, and hGH similar to the control subjects (all *P*>.20).

No significant differences between groups were seen for albumin, potassium, IGF-1, thyroid-stimulating hormone, testosterone, or estrogen (ANOVA $P>.05$ for each).

Relation between hGH and IGF-1. Because IGF-1 is the anabolic mediator of hGH, the relation between the two hormones was studied. The IGF-1/hGH ratio was approximately four times higher in noncachectic CHF patients and control subjects than in cachectic subjects. Because this ratio has a skewed distribution, the log-transformed ratios were compared statistically (control subjects, 2.89±0.25; noncachectic, 3.00±0.16; cachectic, 2.03±0.22, $P=.014$ versus control subjects and $P=.0014$ versus noncachectic subjects).

Predictors of Muscle Wasting

Weight loss. Only in cachectic patients could the documented weight loss be correlated with physiological measures and humoral parameters. Significant correlates of weight loss (in kilograms) in simple regression analysis were TNF-α ($r=.78$, $P=.0003$), reverse T_3 ($r=.61$, $P=.012$), peak $\dot{V}O_2$ ($r=-.54$, $P=.032$). Independent predictors of documented weight loss in a multivariate model with age, TNF-α, reverse T_3, cortisol, norepinephrine, and insulin were TNF-α ($P=.006$) and reverse T_3 ($P=.044$). Predictors of documented weight loss in a stepwise regression model with age, peak $\dot{V}O_2$, and 12 humoral factors were TNF-α in the first step (F value, 22.24; $P<.001$) and testosterone in the second step (F value, 4.13; $P<.025$). Similar results were found when the weight loss was normalized for the previous normal weight (TNF-α versus percent weight loss, $r=.80$, $P=.0002$). When the derived measure of the ratio of IGF-1 and hGH was analyzed together with TNF-α and testosterone, these three variables predicted 83.5% of the variation of the documented weight loss (in kilograms) and 84.7% of the variation of the relative weight loss (in percent) in 16 cachectic CHF patients (see Table 4⊡). It is important to note that neither testosterone nor log IGF-1/hGH significantly correlated with the body mass index or measures of weight loss but that both became (independently of each other) important after adjustment for the effect of TNF.

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Table 4. Stepwise and Multiple Regression Analysis of the Association Between TNF-α and Testosterone Levels and the Ratio of IGF-1 and hGH Levels (log IGF-1/hGH) on Documented Weight Loss in 16 Cachectic CHF Patients

Ideal body weight. In Table 5⊡, we present the results of correlation analysis for percent ideal weight. Significant correlates of lower weight (ie, percent ideal weight) in 53 CHF patients were epinephrine, cortisol, norepinephrine, TNF-α, log IGF-1/hGH ($P<.001$), hGH, and basal insulin (both $P<.01$) but also reverse T_3 ($r=-.34$), age ($r=-.32$), and plasma sodium ($r=-.31$, all $P<.05$).

Predictors of reduced weight in a multivariate model with these 10 parameters were insulin ($P=.036$) and to a lesser extent cortisol ($P=.10$), TNF-α ($P=.13$), and norepinephrine ($P=.20$). In a smaller multivariate model with only these four humoral factors, it was found that they predicted weight changes independently of each other in our CHF population: insulin and cortisol (both

$P<.01$), TNF-α, and norepinephrine (both $P<.05$). Stepwise regression showed that, one after another, these factors contributed significantly to the variation of the weight (all four factors together versus percent ideal weight: $R^2=.501$, $P<.0001$). The inclusion of testosterone did not change the principal outcome of the multivariate and the stepwise regression models for percent ideal weight.

View this table: [in this window] [in a new window] **Table 5.** Relation Between Age and Resting Humoral Factors and Body Weight (Measured in % Ideal Body Weight): Results of Univariate Linear Regression Analysis

Influence of Other Clinical Markers

To investigate the best discriminators for explaining the variations in the degree of neurohormonal activation, patients were subgrouped according to peak $\dot{V}O_2$, NYHA functional class, and LVEF. The main results of these analyses are presented in Fig 1 (catecholamines, cortisol, and TNF-α) and Fig 2 (hGH, IGF, insulin, DHEA) compared with the earlier grouping according to the cachectic state.

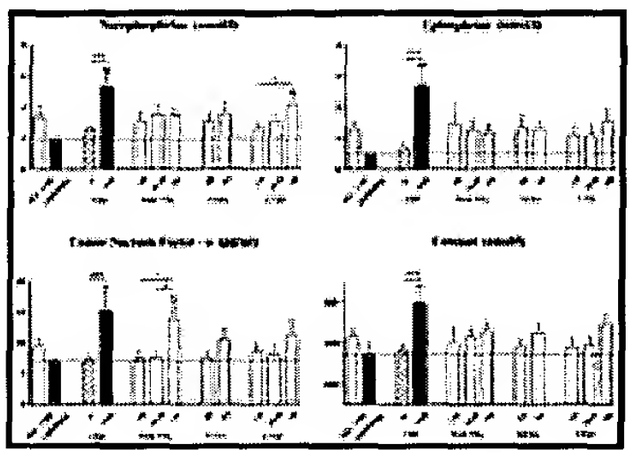

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Figure 1. Levels of catabolic factors (norepinephrine, epinephrine, cortisol, and TNF-α) in 16 healthy control subjects and 53 patients with CHF. Heart failure patients were subgrouped by cachectic state (noncachectic [nc], n=37; cachectic [cach], n=16), peak $\dot{V}O_2$ (<14 [n=17] vs 14 to 20 [n=24] vs >20 mL·kg^{-1}·min^{-1} [n=12]), functional NYHA class (class 1/2 [n=16] vs class 3/4 [n=37]), and LVEF (<20 [n=24] vs 20 to 35 [n=17] vs >35% [n=12]). Probability values for Fisher's test are given if ANOVA showed significant intergroup variation. Data are mean±SEM. *$P<.05$ for intergroup comparison; ***$P<.001$ for intergroup comparison; •$P<.05$ vs control subjects; •• $P<.01$ vs control subjects; and ••• $P<.001$ vs control subjects.

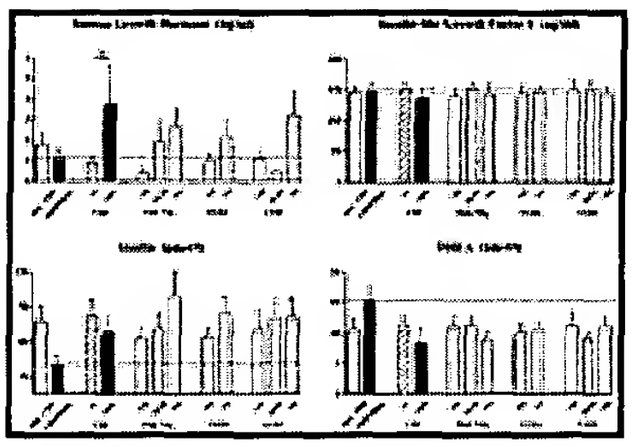

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Figure 2. Levels of anabolic hormones (hGH, IGF-1, insulin, DHEA) in 16 healthy control subjects and 53 patients with CHF. Data are mean±SEM. Subgrouping of heart failure patients and statistical presentation as in legend of Fig 1.

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Peak $\dot{V}O_2$. The CHF patients were stratified according to their peak $\dot{V}O_2$ (<14, 14 to 20, and >20 $mL \cdot kg^{-1} \cdot min^{-1}$). The only significant intergroup difference was observed for creatinine ($P<.01$ for peak $\dot{V}O_2$ <14 [146±14 μmol/L] versus peak $\dot{V}O_2$ 14 to 20 $mL \cdot kg^{-1} \cdot min^{-1}$ [117±12 μmol/L]).

NYHA class. The influence of clinical status as assessed by the functional NYHA classification was analyzed comparing patients in NYHA class 1 or 2 with patients in NYHA class 3 or 4. No significant alterations at the $P<.01$ level could be detected for any of the hormones studied.

LVEF. Stratification of patients according to LVEF was studied (<20% versus 20% to 35% versus >35%). Significant intergroup differences were found only for aldosterone (LVEF <20% [989±177 pmol/L] versus 20% to 35% [462±66 pmol/L] and versus >35% [456±78 pmol/L], both $P<.01$).

It is important to note that for only 2 of the 17 humoral factors (aldosterone and creatinine) were comparisons between groups of CHF patients divided according to NYHA class, LVEF, or peak $\dot{V}O_2$ significant at the $P<.01$ level. If the more stringent Bonferroni correction was applied (17 humoral parameters analyzed; $P<.05/17$, or .00294, considered significant), no significant difference could be found for any comparison. In contrast, the classification into cachectic and noncachectic patients led to substantial differences in many neurohormonal and anabolic/catabolic factors (Table 3, Figs 1 and 2). The results of regression analysis of several hormones and TNF-α versus markers of disease severity in the CHF patients are shown in Table 6 compared with the relation to percent ideal weight.

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Table 6. Univariate Regression Coefficients for the Relation Between Hormones and Cytokines vs Conventional Markers of Severity of CHF and Normalized Body Weight in 53 Patients With CHF

Discussion

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The major finding of this study is that cachexia is associated with hormonal changes in CHF and more conventional measures of severity of CHF are not. Patients with cardiac cachexia demonstrate severe hormonal changes consistent with sympathetic activation and catabolic/anabolic imbalance. These hormonal changes are most clearly demonstrated when patients are subgrouped on the basis of their cachectic status. Several humoral factors are independently related to weight changes in these patients. Subgrouping by cachexia is more predictive of the neurohormonal

status than conventional classifications of severity of CHF. These findings suggest that the catabolic/anabolic disturbance leading to cachexia and the neurohormonal activation are related and of greater importance than the degree of hemodynamic or functional disturbance. Much of the variability in the association of conventional measures of the severity of heart failure and neurohormonal activation, and indeed much of the neurohormonal activation itself, is attributable to cachexia and to the small group of patients with cachexia who are included in many studies.

Definition of Cardiac Cachexia

No agreed-upon definition of cachexia exists, but body fat estimation, anthropometric measurements, predicted percent ideal mass, weight/height index, body mass index, serum albumin, and cell-mediated immunity changes, and especially a weight loss of >10% of the previous normal (ie, "usual") weight, have all been used. Patients have been classified as "malnourished" when the body fat content was <22% in women and <15% in men or when the percentage of ideal weight was <90%.[20] Other groups have defined CHF patients prospectively as "cachectic" when the body fat content was <29% (women) or <27% (men)[6] or when the body weight was <85%[5] or even <80% of ideal.[21]

The development of the cachectic state in CHF could be demonstrated by a longitudinal study in which body weight is measured in a nonedematous state. Including the weight loss as a criterion excludes patients who are constitutionally underweight. Equally, patients initially overweight may be mistakenly classified as cachectic. We used a broad definition of "clinical cardiac cachexia," ie, documented weight loss of ≥5 kg over a period of ≥6 months and a body mass index of ≤24 kg/m^2 observed in patients with CHF without signs of other primary cachectic states. All patients had a weight loss of >7.5% of their previous normal nonedematous body weight. A body mass index of <24 excludes previously obese patients who could merely have lost weight as a consequence of intentional dieting. Because all such definitions are arbitrary, it is important to note that our findings do not differ when the analysis uses different cutoff values for defining cachexia, such as >10% premorbid weight loss (14 patients) or weight loss ≥5 kg and weight <85% of ideal (9 patients).

Development of Cardiac Cachexia

In 1964, Pittman and Cohen,[4] writing about the pathogenesis of cardiac cachexia, stressed the importance of cellular hypoxia to the initiation of less efficient intermediary metabolism, thereby increasing catabolism (protein loss) and reducing anabolism. In addition, they suggested anorexia and increased basal metabolic rate to be the result of a lack of oxygen. Buchanan and colleagues[22] found anorexia that was reversible after mitral valve replacement to be the cause of the cachexia in 11 patients. Neither malabsorption nor cellular hypoxia was of importance. Starvation and anorexia in otherwise healthy persons led to a preferential loss of fat tissue. A study in 27 CHF patients (mean weight, 21% lower than normal)[23] failed to show fat tissue loss but documented an average total body potassium decrease of 35% (a measure of lean tissue independent of body water content). Another study[11] demonstrated increased resting metabolic rates in CHF patients compared with control subjects, a feature of interest given that resting metabolic rate has been shown to correlate with increasing concentrations of catecholamines,[10]

and we have now shown catecholamines to be increased markedly in cardiac cachexia. Physical inactivity and deconditioning have been suggested to be important for the muscle atrophy observed in many CHF patients,[24] but recent histological evidence suggests that the atrophy in states of reduced activity is different from the muscle atrophy observed in CHF.[25] [26] This is also supported by the finding that the duration of heart failure was not different in cachectic and noncachectic patients. In contrast to the commonly held belief, albumin levels were not decreased in the cachectic patients. This would argue against a major contribution of gastrointestinal malabsorption or liver synthetic dysfunction in these patients.

Catabolic Factors

In the 1930s, the existence of an unexplained pyrogen as a product of anaerobic metabolism in cases of fever in heart failure was suggested.[27] In 1990, Levine and colleagues[5] reported that TNF-α is increased in patients with cardiac cachexia. Increased TNF-α has been confirmed by others[6] [7] and in the present study. TNF-α is one of the key cytokines important to the development of catabolism. Animal experiments have shown that the implantation of TNF-α–producing tumor cells in skeletal muscle causes muscle wasting, whereas TNF-α–producing cells in the brain caused marked anorexia.[8] This shows that increased levels of TNF-α may indeed play a causative role in the development of cachexia but also that the site of the production and action of TNF-α modifies its effect. The failing human heart can directly produce TNF-α.[28] Whether this relates to the development of cardiac or general muscle wasting is not known. The new finding of this study is that cytokine activation is only one pathway of those closely related to the degree of wasting and that after adjustment for the influence of TNF, an indirect measure of growth hormone resistance (ie, log IGF-1/hGH) and testosterone levels also seem to be of importance.

Many studies have investigated catecholamine levels in CHF patients. Plasma norepinephrine may reflect overall sympathetic activity,[29] and both norepinephrine and epinephrine can cause a catabolic metabolic balance.[10] [30] Since the original observation in 1962 of increased catecholamines in CHF,[31] no study has investigated catecholamine levels specifically in cachectic CHF patients. Only cachectic CHF patients showed markedly increased norepinephrine and epinephrine levels, with noncachectic CHF patients having near-normal levels (Table 3). None of the three other methods of stratifying the 53 CHF patients revealed significant changes between different groups of CHF patients. This suggests a specific association between cachexia and sympathetic activation in CHF. Another hormone considered to be part of the general stress response with a catabolic action is cortisol.[32] In untreated severe CHF patients, Anand et al[12] demonstrated a 2.5-fold increase of cortisol, probably due to an increase in the release of adrenocorticotropic hormone.[33] The cachectic patients in our study had a 2-fold increase. No other subgrouping of the CHF patients revealed any significant effect on mean cortisol levels.

Anabolic Hormones

We studied several anabolic hormones such as sex steroids (testosterone, DHEA, and estrogen), hGH, IGF-1, and insulin. We looked for counterregulatory increases of anabolic factors in cachectic CHF patients. Only hGH was increased (Table 3). Anand et al[12] demonstrated such an

increase of hGH in untreated patients with severe CHF. The role of hGH in CHF is unclear, because it has both direct and indirect effects. Directly, it acts on lipid metabolism (catabolic), but normally its major (anabolic) effect is indirect via the somatomedins (the main hGH-dependent somatomedin is IGF-1). By this mechanism, hGH acts in an insulin-like manner (ie, anabolic on cell proliferation and protein synthesis) and is opposed to the actions of cortisol.[34] Because the increase in hGH in our cachectic patients was not accompanied by an increase of IGF-1, this suggests the presence of growth hormone resistance, and via its direct action, hGH could then even promote increased catabolism. These findings merit further investigation.

Insulin is considered to be the most powerful physiological anabolic hormone. In stable CHF patients, we have previously described the development of insulin resistance along with increases of basal insulin levels.[13] Cardiac cachectic patients showed slightly reduced insulin levels compared with noncachectic patients but increased levels compared with normal control subjects. There were no significant changes of testosterone or estradiol levels. Interestingly, the mean concentration of the anabolic hormone DHEA was reduced in all heart failure patients as well as in the subgroup of cachectic CHF patients compared with control subjects (both trends with $P<.05$, Table 3).

Catabolic/Anabolic Imbalance

In cachectic CHF patients, factors that are acting to increase protein and fat tissue degradation and stimulate energy production are increased (norepinephrine, epinephrine, cortisol, TNF-α), whereas anabolic factors either respond inadequately to cachexia (DHEA is reduced in most severely cachectic patients; testosterone does not increase) or appear to develop a resistance syndrome (growth hormone). This suggests that the syndrome of cardiac cachexia is characterized by a severe catabolic/anabolic imbalance in favor of catabolic metabolism, which may be a valid target for novel therapeutic interventions. It is unlikely that any single physical or biochemical disorder causes cardiac cachexia in all patients.

We found no marked reduction of albumin levels in our cachectic patients compared with control subjects, which is to some degree unexpected. The diuretic doses were similar in the two patient groups. The liver function of the cachectic and noncachectic CHF patients appeared to be normal. Therefore, we do not believe that the albumin results are likely to reflect impaired hepatic albumin synthesis accompanied by decreased blood volume due to diuretics. Taken together, the results argue against a major impact of anorexia and starvation in the majority of these cachectic CHF patients.

Limitations

The present study is a cross-sectional study. The differences have been described, but changes over time have not been shown. The proof of causality requires a prospectively designed longitudinal study. For clarity of presentation, we subdivided patients into categories of increasing severity. This was arbitrary, but similar conclusions can be drawn when the classification of severity was analyzed using all individual points in regression analysis. Table 5 shows strong inverse relationships between several increased hormones and TNF and reduced

body weight that cannot be found with conventional severity markers (Table 6). One of the strengths of the present investigation is also one of its limitations: the multiple biochemical investigations. We chose 17 humoral factors that characterize heart failure severity, catabolism, or anabolism and investigated 69 subjects in three groups. Necessarily, we performed many statistical tests. We reduced the level of significance by a factor of 5 from 5% to 1%, protecting against chance findings. Because the results have a physiological explanation, we believe that our results are indicative. Finally, many other interesting and possibly causally important factors were not included in our analysis, for example, prostaglandins, interferons, interleukins and soluble TNF receptors, adhesion molecules, hGH- and IGF-binding proteins, sex hormone–binding globulin, atrial natriuretic peptide, and endothelins. This study was performed only in male CHF patients, because sex steroid levels are not comparable in men and women. Therefore, it is difficult to draw conclusions on the development of cardiac cachexia in women, but we have no reason to believe that the general pattern of stress responses and immune activation would be different in women. We are aware that several hormones intercorrelate, and this may influence the outcome of the statistical analysis. For instance, it is known that cytokines may inhibit testosterone synthesis,[35] which suggests an inverse relationship between these two parameters. This was not found when our population was analyzed as a whole, but it is indeed present in the subgroup of cachectic patients (data not presented).

Conclusions

Catabolic/anabolic disturbance and hormonal activation are relevant to the development of cardiac cachexia. In an extension of the neurohormonal hypothesis,[1] which postulates that heart failure progresses because activated endogenous neurohormonal systems exert a deleterious effect on the heart and circulation, this study suggests that the syndrome of heart failure progresses to cardiac cachexia when the normal metabolic balance of catabolism and anabolism is altered.

Selected Abbreviations and Acronyms

CHF	= chronic heart failure
hGH	= human growth hormone
IGF-1	= insulin-like growth factor-1
LVEF	= left ventricular ejection fraction
PRA	= plasma renin activity
T_3	= triiodothyronine
TNF	= tumor necrosis factor

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Footnotes

Reprint requests to Dr Stefan Anker, Cardiac Medicine, National Heart and Lung Institute London, Imperial College School of Medicine, Dovehouse St, London SW3 6LY, UK.

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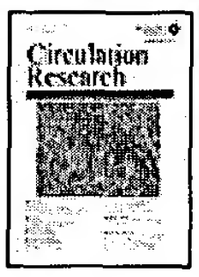

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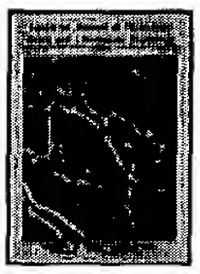

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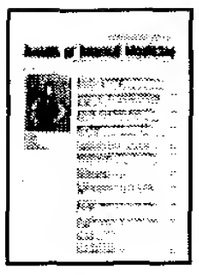

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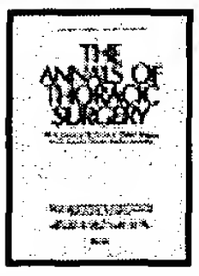

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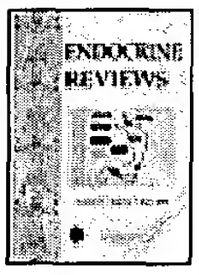

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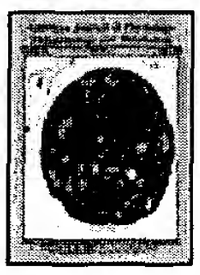

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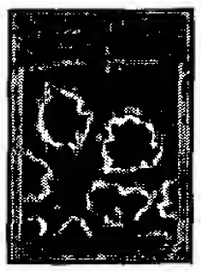

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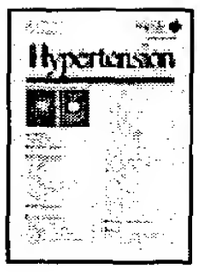

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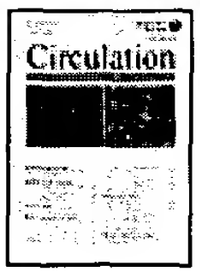

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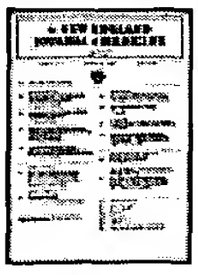

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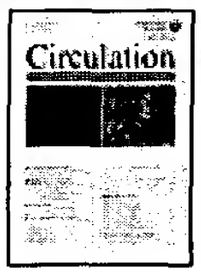

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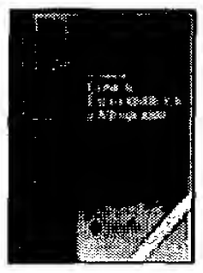

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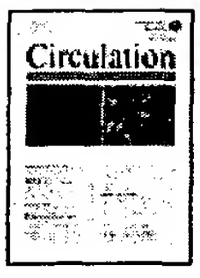

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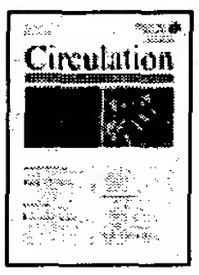

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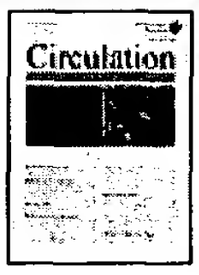

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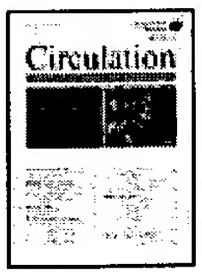

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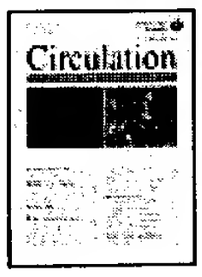

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(*Circulation.* 1997;96:1501-1506.)

Articles

Modulation of Cytokine Production and Protection Against Lethal Endotoxemia by the Cardiac Glycoside Ouabain

Akira Matsumori, MD, PhD; Koh Ono, MD; Ryosuke Nishio, MD; Hideki Igata; B Pharm; Tetsuo Shioi, MD, PhD; Shigeo Matsui, MD; Yutaka Furukawa, MD; Atsushi Iwasaki, MD; Yoshisuke Nose, MD; ; Shigetake Sasayama, MD, PhD

From the Department of Cardiovascular Medicine, Kyoto University, Kyoto, Japan, and Hyogo Red Cross Blood Center (Y.N.).

Correspondence to Akira Matsumori, MD, PhD, Department of Cardiovascular Medicine, Kyoto University, 54 Kawaracho Shogoin, Sakyo-ku, Kyoto 606, Japan. E-mail amat@kuhp.kyoto-u.ac.jp

Abstract

Background Recent studies have shown that cytokines are capable of modulating cardiovascular function and that some drugs used in the treatment of heart failure variably modulate the production of cytokines. To examine whether cardiac glycosides also modulate cytokine production, we evaluated the effects of ouabain on the production of cytokines in vitro and in vivo.

Methods and Results Human peripheral blood mononuclear cells (PBMC) were obtained from healthy volunteers. PBMC were cultured with or without ouabain in the presence or absence of lipopolysaccharide (LPS). Ouabain induced the production of interleukin (IL)-1ß, IL-6, and tumor necrosis factor (TNF)-α in PBMC and induced mRNA of these cytokines, an induction apparently at the transcriptional level. Amiloride, staurosporin, and genistein inhibited cytokine production, and protein kinase C and tyrosine kinase appeared to be involved in the modulation

of cytokine production induced by ouabain. However, when PBMC were stimulated with LPS, ouabain suppressed the production of IL-6 and TNF-α. To investigate whether ouabain modulates cytokine production in vivo, we evaluated the effects of ouabain in LPS-treated mice. Ouabain was found to protect against LPS-induced lethal toxicity in mice and decreased circulating IL-6 and TNF-α levels in vivo.

Conclusions These previously unrecognized immunomodulating effects of a cardiac glycoside may explain either the beneficial or the detrimental effects of these drugs in heart failure patients.

Key Words: heart failure • interleukins • tumor necrosis factor • inotropic agents • shock

Introduction

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Since William Withering described the use of cardiac glycosides in his classic monograph on the pharmacology of the leaves of the common foxglove plant (*Digitalis purpurea*) in 1785,[1] these agents have played a prominent role in the treatment of congestive heart failure. However, as long ago as the turn of the last century a controversy emerged regarding their efficacy and appropriate indications. The ability of digoxin to improve symptoms in patients with heart failure has been confirmed in two recently published withdrawal trials[2,3]; but, unlike vasodilators, the angiotensin-converting enzyme inhibitors, in particular cardiac glycosides, have not been shown to improve survival in patients with congestive heart failure, perhaps because the trials were too small to detect any but very large positive or negative effects on mortality. The results of the multicenter trial by the Digitalis Investigation Group, published recently, indicate that in a large population of patients with heart failure, long-term treatment with digoxin has no significant effect on overall mortality, though it reduced the overall rate of hospital admissions and that for worsening heart failure.[4]

Recently developed inotropic agents that increase the intracellular levels of cAMP, either by stimulating ß-adrenergic receptors or by inhibiting phosphodiesterase, have produced short-term hemodynamic improvements in patients with advanced heart failure. However, the results of long-term treatment with such agents have been mixed.

In our experimental model of congestive heart failure caused by viral myocarditis, vesnarinone improved survival and reduced myocardial damage, but survival was not improved by amrinone. These agents modulate natural killer cell activity in different ways.[5] Furthermore, recent studies from our laboratory showed that drugs used to treat heart failure variably modulated the production of cytokines.[6,7,8] Those experiments also suggested that some immunomodulatory effects of these drugs were pertinent to their effects in heart failure patients. This study was performed to investigate whether cardiac glycosides modulate cytokine production. Specifically, we evaluated the effects of ouabain on the production of cytokines in vitro and in vivo.

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Preparation of Human Peripheral Blood Mononuclear Cells

PBMC were obtained from healthy volunteers. PBMC were isolated by Ficoll-paque density centrifugation. The collected cells were washed three times with PBS, finally resuspended in RPMI 1640 medium (Gibco) supplemented with 10% heat-inactivated fetal calf serum (Gibco), 100 U/mL penicillin, 100 µg/mL streptomycin (Gibco), and 50 µmol/L 2-mercaptoethanol, and cultured at 37°C in a humidified 5% CO_2 atmosphere.

Effects of Ouabain on the Production of Cytokines by PBMC

Ouabain (Sigma) was dissolved in distilled water. After incubation of the PBMC ($2x10^6$ cells/mL in 24-well plates, n=6 wells, from 2 subjects) with ouabain for 24 hours, the supernatants were harvested and stored at -80°C until cytokine assay. IL-1ß, IL-6, and TNF-α levels in the culture supernatants were determined by specific ELISA kits (Otsuka Pharmaceutical Co).

To test the possible role of Na^+/H^+ or Na^+/Ca^{2+} exchanger in the induction of cytokines by ouabain, PBMC were treated with amiloride, an inhibitor of the Na^+/H^+ and Na^+/Ca^{2+} exchanger. Furthermore, the influence of ouabain on the transcription of cytokine mRNA was examined by measuring the production of cytokine in the presence of actinomycin D, which inhibits transcription. Finally, the modulation of ouabain-induced cytokine production by PK was examined by exposing the media to the PK inhibitors staurosporin and genistein. Amiloride, actinomycin D, staurosporin, and genistein (Sigma) were dissolved in 0.1% DMSO and diluted with the medium. This concentration of DMSO did not influence the production of cytokine by PBMC. PBMC were incubated with the agents in the presence of 10^{-7} mol/L ouabain for 24 hours, and supernatants were harvested for IL-1ß, IL-6, and TNF-α assay.

To investigate the effects of ouabain on the LPS-induced cytokine production, PBMC were stimulated with 1 µg/mL of LPS (Difco) immediately after administration of ouabain. After 24 hours of incubation the supernatants were harvested. Significant interindividual variability in cytokine production in response to LPS was observed. Therefore, we measured the cytokine production by PBMC from 3 subjects and in 2 wells from each individual.

Effects of Ouabain on mRNA Expression of IL-1ß, IL-6, and TNF-α of PBMC

These experiments were performed to study the effect of ouabain on the induction of cytokine mRNA with the Northern blot analysis method. PBMC were cultured as described above with or without ouabain in the presence or absence of LPS and harvested 6 hours after incubation. Total RNA was isolated by a guanidinium thiocyanate/phenol/chloroform/isoamylalcohol procedure and quantitated by spectrophotometry. To minimize variance in the yield of RNA, each sample was pooled from three independent cultures. Ten micrograms of total RNA was electrophoresed on a 1.2% agarose-formaldehyde gel transferred to a nylon membrane (Gene Screen, NEN Research Products) and successively hybridized with cDNA probes for IL-1ß, IL-6, TNF-α, and

GAPDH. Recombinant cDNA clone obtained from the American Type Culture Collection (Rockville, Md) was used to prepare the DNA probe. Quantification of the RNA message was performed with the use of a Fujix BAS 2000 image analyzer with normalization to GAPDH message levels.

Effects of Ouabain on LPS-Treated Mice

The effects of ouabain on plasma IL-1ß, IL-6, and TNF-α levels were studied in 8-week-old female BALB/c, LPS-treated mice (Shizuoka Agricultural Cooperation Association, Shizuoka, Japan). Each animal received 1 mg/kg IP of ouabain immediately after the injection of 250 µg of LPS. After 1, 2, or 4 hours, the mice were bled by orbital puncture, and the plasma concentration of IL-1ß, IL-6, and TNF-α was determined by the ELISA method (6 mice per each 1-, 2-, or 4-hour period of time).

To study the effect of ouabain on LPS-induced lethal toxicity, 8-week-old female BALB/c mice each received 0.1 (n=20) or 1 (n=20) mg/kg IP of ouabain immediately after the injection of 250 µg IP of LPS.

Statistical Analysis

Statistical comparisons of cytokine production were performed by ANOVA followed by Fisher's protected least significant difference test for multiple samples comparison. The comparison of the data on the effect of ouabain-induced cytokine production by amiloride, actinomycin D, and PK inhibitors was performed by Mann-Whitney *U* test because the data included below-detectable levels. Kaplan-Meier plots were made of the survival data, and survival differences between the control and active treatment were tested by the Mantel-Cox log rank test. Data are expressed as mean±SE. A value of $P<.05$ was considered statistically significant.

Results

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Effects of Ouabain on the Production of Cytokines by PBMC

Ouabain caused a prominent increase in IL-1ß production in concentrations of 10^{-7} mol/L (29.0±3.0 versus 0.4±0.1 ng/mL at baseline, $P<.01$) and higher (Fig 1A). In contrast, induction of IL-6 and TNF-α by ouabain occurred at a concentration of 10^{-7} mol/L only, with a small increase in its production from a baseline value of 0.7±0.2 ng/mL to a peak of 1.1±0.1 ng/mL and a significant increase in TNF-α from a baseline value of 0.3±0.1 ng/mL to a peak of 2.3±0.5 ng/mL ($P<.01$). Exposure of the media to amiloride significantly inhibited the ouabain-induced production of IL-1ß, IL-6, and TNF-α (Table 1). Likewise, treatment of PBMC with actinomycin D reduced the production of IL-1ß and IL-6 and tended to decrease TNF-α production (Table 1). A variable modulation of cytokine production by PK was observed. The PKC inhibitor staurosporin increased production of IL-1ß and IL-6 in lower concentrations but decreased their production in higher concentrations. Staurosporin inhibited TNF-α production in all concentrations tested. The protein tyrosine kinase inhibitor genistein increased the production of IL-1ß in lower concentrations and

inhibited it in higher concentrations, whereas the production of both IL-6 and TNF-α were inhibited in both concentrations (Table 2).

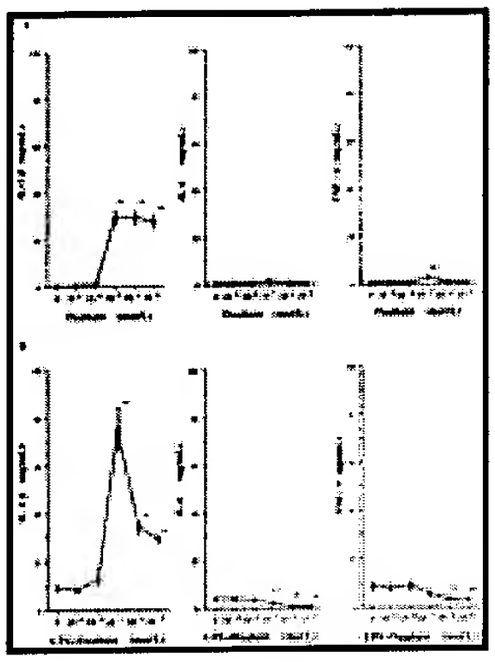

Figure 1. A, Effects of ouabain on the production of IL-1ß, IL-6, and TNF-α by PBMC. B, Effects of ouabain on the production of IL-1ß, IL-6, and TNF-α by PBMC stimulated with LPS. See text for discussion. Each value represents mean±SE of six determinations. $^{**}P<.01$ vs baseline measurements.

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View this table: [in this window] [in a new window] **Table 1.** Effect of Amiloride and Actinomycin D on Ouabain-Induced Cytokine Production

View this table: [in this window] [in a new window] **Table 2. Effect of Protein Kinase Inhibitors on Ouabain-Induced Cytokine Production**

Effects of Ouabain on the LPS-Induced Cytokine Production by PBMC

Ouabain caused a concentration-dependent reduction in LPS-stimulated IL-6 and TNF-α release, a decrease that became statistically significant at a concentration of 10^{-7} mol/L (Fig 1B). In contrast, ouabain enhanced IL-1ß production, which reached its peak at 10^{-7} mol/L (Fig 1B).

Effects of Ouabain on mRNA Expression of IL-1ß, IL-6, and TNF-α of PBMC

Exposure to 10^{-7} mol/L ouabain markedly increased the accumulation of IL-1ß, IL-6, and TNF-α mRNA (Fig 2). At 6 hours, IL-1ß, IL-6, and TNF-α mRNA had increased by 4.6-fold, 3.2-fold, and 1.2-fold, respectively. LPS also increased the accumulation of IL-1ß, IL-6, and TNF-α mRNA. However, the induction of cytokine mRNA by LPS was significantly inhibited in the presence of 10^{-6} mol/L ouabain.

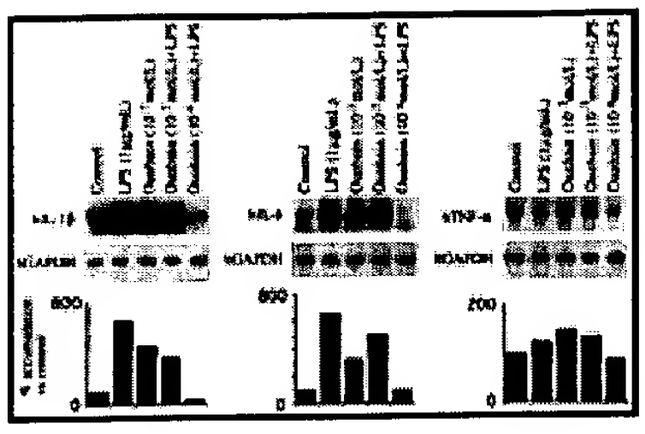

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Figure 2. Northern blot analysis of mRNA of IL-1ß, IL-6, and TNF-α of PBMC. See text for discussion. Data are representative of three separate experiments performed at 6 hours.

Effects of Ouabain on LPS-Treated Mice

In the absence of ouabain, LPS induced a rapid increase in the plasma concentrations of IL-6 and TNF-α within 1 hour. The administration of 1 mg/kg ouabain immediately after injection of LPS inhibited the increase in both (Fig 3). LPS induced only a slight increase in the plasma IL-1ß (0.22±0.07, 0.26±0.04, and 0.38±0.09 ng/mL at 1, 2, and 4 hours, respectively), which was not significantly inhibited by ouabain.

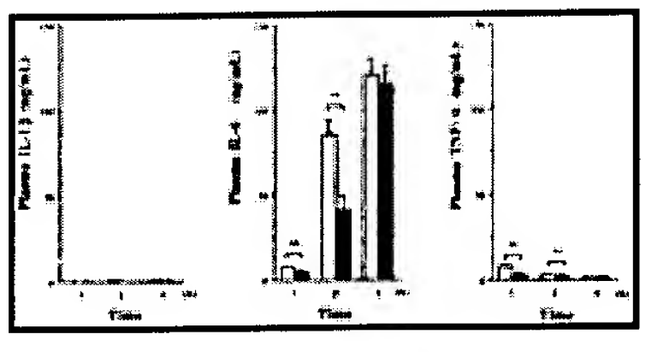

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Figure 3. Effects of ouabain on plasma IL-1ß, IL-6, and TNF-α levels in LPS-treated mice. Open bars represent experiments with LPS only; solid bars represent experiments with LPS+ouabain. See text for further discussion. Each value represents mean±SE of six determinations. $^{**}P<.01$.

At the dose of 250 µg per mouse, LPS caused death in 95% of the animals within 48 hours. The administration of 1 mg/kg ouabain immediately after administration of LPS significantly reduced this mortality. This protective effect of ouabain, however, was dose dependent and was not observed with the lower dose of 0.1 mg/kg (Fig 4).

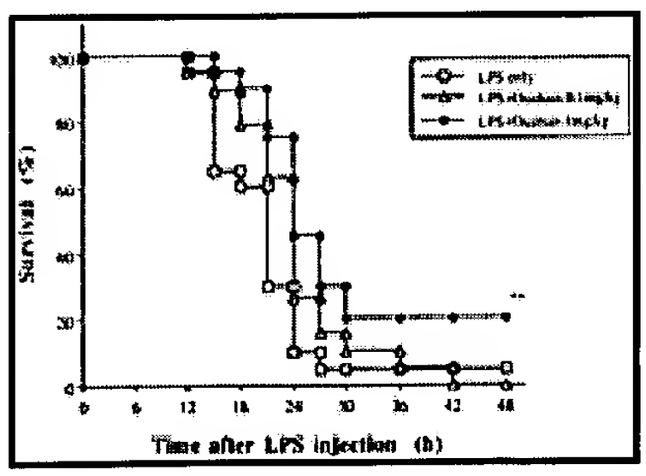

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Figure 4. Effect of ouabain on LPS-induced lethal toxicity in mice. See text for discussion. $^{**}P<.01$, LPS+ouabain 1 mg/kg vs LPS only.

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Discussion

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Ouabain and related cardiac glycosides are highly specific inhibitors of Na^+/K^+-ATPase. This enzyme (the sodium pump) catalyzes the coupled active transport of Na^+/K^+ across the plasma membranes of most animal cells.[9] It is well established that the positive inotropic effect of a cardiac glycoside on the myocardium is due to the partial inhibition of the cardiac Na^+/K^+-ATPase, causing a small increase in intracellular Na^+, which in turn affects the sarcolemmal Na^+/Ca^{2+} exchanger, leading to an increase in intracellular Ca^{2+} and in the force of contraction.[10] [11] [12] This effect on cardiac contractility is the basis for the main role of these drugs in the treatment of congestive heart failure.

Modulation of intracellular ion balance by Na^+/K^+-ATPase is an important mechanism by which cell growth and/or differentiation can be regulated. It has been reported that inhibition of Na^+/K^+-ATPase by ouabain can induce RNA encoding of the growth factors, IL-6, and macrophage colony–stimulating factor through what appears to be a calcium-dependent mechanism.[13] [14] Ouabain also has been shown to increase c-*fos* and c-*jun* transcription in a variety of cultured cells including myocytes.[15] [16] Induction of c-*fos* by ouabain appears to involve PKC, but the mechanism of PKC activation by ouabain has not been clarified. Previous studies have demonstrated that both inotropic and toxic concentrations of ouabain enhance phosphoinositide turnover, increase diacylglycerol content, and activate PKC.[17] [18] While these effects may be the consequence of activation of phospholipase C by ouabain-induced increases in intracellular Ca^{2+},[17] there is also some evidence to suggest that activation of PKC by ouabain may occur by unidentified mechanisms independent of a ouabain-induced rise in intracellular Ca^{2+}.[18]

In this study we found that the cardiac glycoside ouabain induced production of IL-1ß, IL-6, and TNF-α in human PBMC. Ouabain induced mRNA of these cytokines, and the induction appeared to be at the transcriptional level. Amiloride, staurosporin, and genistein inhibited cytokine production. Therefore, PKC and tyrosine kinase are thought to be involved in the modulation of cytokine production induced by ouabain and to have differential effects on the production of these cytokines.

Sepsis and septic shock result primarily if not exclusively from excessive stimulation of the host immune system, especially macrophages, by the complex glycolipid (LPS, endotoxin), which resides in the outer membrane of bacteria. LPS stimulates immunocytes, mainly macrophages, to generate IL-1, IL-6, TNF-α, prostanoids, leukotrienes, and nitric oxide. Accordingly, we studied the effects of ouabain on cytokine production by LPS-stimulated PBMC. When PBMC were stimulated with LPS, ouabain suppressed the production of IL-6 and TNF-α. Ouabain protected

against LPS-induced lethal toxicity in mice and decreased circulating IL-6 and TNF-α levels in vivo. LPS initiates signaling from the plasma membrane to the nucleus, which involves activation of PKC, PKA, and the Na^+/H^+ exchanger[19 20] and an increase in the number of K^+ channels,[21] though the signal transduction pathways are not completely understood. Furthermore, the mechanism of modulation of LPS-induced IL-1ß, IL-6, and TNF-α production by ouabain is not clear, although these findings suggest that ouabain may variably regulate the production of these cytokines.

The dosages of ouabain used in murine experiments are higher than the dosages that are currently used to treat heart failure patients. It is difficult to compare dosages in different animal species; however, on the basis of body surface area, a given dosage in mice is comparable with a dosage about 12-fold lower in humans.[22] Thus, a dosage of 1 mg/kg in mice is equivalent to 0.08 mg/kg in humans.

A growing body of literature suggests that cytokines are capable of modulating cardiovascular function.[23] Concentrations of TNF-α are increased in patients with chronic heart failure,[24 25] and TNF-α has been reported to depress myocardial contractility.[26 27 28] Although the effect of IL-1 on cardiac function is controversial, IL-1 has also been demonstrated to decrease cardiac contractility.[29 30 31] Furthermore, IL-1ß, TNF-α, and interferon-γ have cytotoxic effects on cultured cardiac myocytes.[32] In addition to these humoral effects, these cytokines may activate cytotoxic T cells, which may cause direct injury to myocytes.[33] More recently, IL-1ß has been shown to cause myocyte hypertrophy associated with induction of fetal genes.[34] IL-6 may exert a negative inotropic effect,[26] and mice overexpressing both IL-6 and IL-6 receptors have been found to develop cardiac hypertrophy.[35]

Recent observations suggest that growth abnormalities that accompany hypertrophy of the overloaded myocardium may play an important role in the deterioration of the condition of patients with chronic heart failure.[36] As IL-1 and IL-6 may play important roles in the development of cardiac hypertrophy,[34 35] these cytokines may be involved in potentially important maladaptive mechanisms that develop in advanced heart failure. In the present study, ouabain induced the production of IL-6 and TNF-α but suppressed their induction in a stimulated condition in vitro. Furthermore, ouabain inhibited the production of IL-6 and TNF-α in a murine model of endotoxemia in vivo. Thus, ouabain may have different effects on cytokine production in the unstimulated condition and in the immunologically activated state. It is difficult to compare the effects of drugs among different species, but it is important to note that variable effects of ouabain on the production of cytokines were seen in vitro and in vivo.

Studies similar to those reported here need to be performed in humans, given the significant differences in some of the responses of animals and of humans. Assuming that the present findings can be extrapolated to patients with congestive heart failure, digitalis glycosides may have different effects on the production of cytokines among those with and those without immune activation. Until the nature of these previously unrecognized effects of cardiac glycosides is

clarified, however, whether the modulation of cytokine production is a part of the beneficial or of the undesirable effects of these drugs in heart failure patients will remain uncertain. These questions may be pertinent to the current efforts aiming at reassessing the value of cardiac glycosides and related drugs in the treatment of heart failure.

Selected Abbreviations and Acronyms

IL	= interleukin
LPS	= lipopolysaccharide
PBMC	= human peripheral blood mononuclear cells
PK; PKA; PKC	= protein kinase(s); protein kinase A; protein kinase C
TNF	= tumor necrosis factor

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[Abstract] [Full Text] [PDF]

European Journal of Biochemistry ▸HOME

Z. Xie and A. Askari
Na+/K+-ATPase as a signal transducer
Eur. J. Biochem., May 15, 2002; 269(10): 2434 - 2439.
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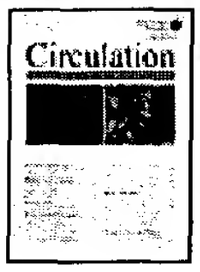

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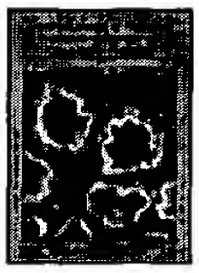

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L6            0 L2 AND REDUCE LPS

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L8           47 L1 AND LPS

=> s l8 and treatment
L9            7 L8 AND TREATMENT

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L10  ANSWER 1 OF 6     MEDLINE on STN                    DUPLICATE 1
2004283437.    PubMed ID: 15182775.   Selective intestinal decontamination in
     advanced chronic heart failure: a pilot
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     Hendrik K; Ieven Margaretha M; Bosmans Johan M; Schuerwegh Annemie; Bridts
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Chris H; Wuyts Floris; Stevens Wim J; Anker Stefan D; Rauchhaus Mathias; Vrints Christiaan J. (Department of Cardiology, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium.) European journal of heart failure : journal of the Working Group on Heart Failure of the European Society of Cardiology, (2004 Jun) 6 (4) 483-91. Journal code: 100887595. ISSN: 1388-9842. Pub. country: Netherlands. Language: English.

AB Background and aims: Endotoxin, derived from intestinal aerobic Gram-negative bacilli (AGNB), could be an important monocyte activator in **chronic heart failure** (CHF). The effect of selective decontamination of the digestive tract (SDD) on intracellular monocyte cytokine production, monocyte CD14 expression, circulating endotoxin and cytokines, and flow-mediated dilation (FMD) was studied in patients with severe CHF. Methods and results: Ten patients with CHF (NYHA class III-IV) were enrolled in a non-placebo controlled pilot trial involving the administration of SDD (polymyxin B, tobramycin) for 8 weeks. One patient was later excluded due to cardiac transplantation. Before **treatment**, after 4 and 8 weeks therapy, and 6 weeks post-**treatment**, monocyte CD14 expression, intracellular monocyte production of interleukin-1beta [IL-1beta], interleukin-6 [IL-6], tumour necrosis factor (TNF)-alpha with and without lipopolysaccharide (**LPS**) stimulation were measured. Concentrations of endotoxin and cytokines (IL-1beta, IL-6, TNF-alpha) were also determined. AGNB in faeces, intestinal endotoxin and FMD were assessed at baseline, after 4 weeks of **treatment** and 6 weeks post-**treatment.** SDD eradicated intestinal AGNB (P<0.00001) and decreased faecal endotoxin concentrations (P<0.00001). There was a significant decline in monocyte CD14 expression (P=0.03) and in IL-1beta (P=0.0001), IL-6 (P=0.02) and TNF-alpha (P=0.0002) production after 4 and 8 weeks of **treatment** in the basal state and for IL-1beta (P=0.008) and IL-6 (P=0.005) after **LPS** stimulation. FMD significantly improved at 4 weeks and returned to baseline after **treatment** discontinuation (P=0.002). Circulating concentrations of endotoxin and cytokines remained unchanged. Conclusion: Reduction of the intestinal endotoxin pool led to a decrease in monocyte CD14 expression and intracellular cytokine production in patients with severe CHF. The improvement of peripheral endothelial function could be a marker of the anti-inflammatory effect of SDD.

L10 ANSWER 2 OF 6 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2003:576101 The Genuine Article (R) Number: 697RP. Myocardial IL-6 regulation by neurohormones - an in vitro superfusion study. Jeron A (Reprint); Kaiser T; Straub R H; Weil J; Riegger G A J; Muders F. Klinikum Univ Regensburg, Klin & Poliklin Innere Med 2, Franz Josef Strauss Allee 11, D-93042 Regensburg, Germany (Reprint); Klinikum Univ Regensburg, Klin & Poliklin Innere Med 2, D-93042 Regensburg, Germany; Klinikum Univ Regensburg, Klin & Poliklin Innere Med 1, D-93042 Regensburg, Germany. BRAIN BEHAVIOR AND IMMUNITY (AUG 2003) Vol. 17, No. 4, pp. 245-250. Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA. ISSN: 0889-1591. Pub. country: Germany. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Interleukin-6 (IL-6) is expressed in the myocardium and has been implicated in cell proliferation, negative inotropic effects and myocardial hypertrophy. To determine whether myocardial IL-6 is modified by neuro-humoral and immunoregulatory stimuli, we studied the effects of lipopolysaccharide (**LPS**), corticosterone (CS), isoproterenol and angiotensin II on myocardial IL-6 secretion in superfused myocardium.

Methods: Slices of rat left ventricular myocardium were superfused in 80 mul chambers for up to 5 h. **LPS** (1, 50, and 100 mug/ml), CS (10(-7), 10(-6), and 10(-5) M, DSMO as vehicle), isoproterenol (10(-6), 10(-7), and 10(-8) M) and angiotensin II (10(-5), 10(-7), and 10(-9) M) were added to the culture medium at hour 2. IL-6 was measured in the perfusate by ELISA.

Results: Physiological corticosterone concentrations (10(-7) M) resulted in an increase in IL-6 concentration (142%) while high doses of steroid decreased IL-6 significantly (CS 10(-6) M: 88 +/- 14%, p <.05; CS

10(-5): 91 +/- 9%, p < .05) after 5 h. Left ventricular IL-6 secretion was significantly stimulated by **LPS** 50 mug/ml (3262 1684% vs. CTRL: 116 +/- 134%, p < .01). Isoproterenol **treatment** increased in IL-6 secretion compared to controls with and without CS, while angiotensin II reduced IL-6 concentration only in combination with CS.

Conclusion: Myocardial IL-6 secretion is modulated by physiological concentrations of corticosterone or angiotensin II and can be induced by **LPS** or isoproterenol, indicating a tight regulation of this cytokine. Suppression of cytokine expression within the heart might be a potential therapeutic goal in the **treatment** of various cardiovascular diseases.

L10 ANSWER 3 OF 6 EMBASE
on STN

2002294975 EMBASE Effect of interleukin-10 on the production of tumor necrosis factor-alpha by peripheral blood mononuclear cells from patients with **chronic heart failure.** Bolger A.P.; Sharma R.; Von Haehling S.; Doehner W.; Oliver B.; Rauchhaus M.; Coats A.J.S.; Adcock I.M.; Anker S.D.. A.P. Bolger, Department of Clinical Cardiology, National Heart and Lung Institute, London SW3 6LY, United Kingdom. a.bolger@ic.ac.uk. American Journal of Cardiology 90/4 (384-389) 15 Aug 2002.
Refs: 29.
ISSN: 0002-9149. CODEN: AJCDAG.
Publisher Ident.: S 0002-9149(02)02494-3. Pub. Country: United States.
Language: English. Summary Language: English.

AB **Chronic heart failure** (HF) is a state of inflammatory immune activation characterized by elevated circulating levels of tumor necrosis factor-α (TNF-α). Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine that inhibits TNF-α production and lessens endotoxin bioactivity. It is not known whether IL-10 reduces lipopolysaccharide (**LPS**) stimulated TNF-α production of peripheral blood mononuclear cells (PBMCs) from patients with chronic HF. PBMCs were isolated from 15 patients with chronic HF (New York Heart Association functional class 3.0 ± 0.2, left ventricular ejection fraction 30 ± 2%, peak oxygen consumption 18.1 ± 0.8 ml/kg/min) and 15 healthy control subjects and stimulated with 1 and 10 ng/ml **LPS** for 24 hours with or without prior addition of IL-10 (10 ng/ml). TNF-α was quantified in cell-free supernatants by an enzyme-linked immunosorbent assay. TNF-α, soluble TNF receptors, IL-10, and **LPS** were quantified in plasma. **LPS** stimulated TNF-α production was highest in those patients in New York Heart Association class II (p <0.01 vs New York Heart Association class III and IV, p <0.001 vs control subjects). IL-10 reduced PBMC TNF-α production in all stimulated samples at 1 and 10 ng/ml **LPS** (mean reduction 43% at 1 ng/ml, p <0.01 and 55% at 10 ng/ml, p <0.0001). The percentage reduction in TNF-α release did not differ significantly between patients and control subjects or with respect to severity of chronic HF or baseline immune parameters. Independently of clinical severity, IL-10 profoundly inhibits TNF-α release from PBMCs isolated from patients with chronic HF. IL-10 is, therefore, a potential therapy for use in chronic HF associated with inflammatory immune activation.

L10 ANSWER 4 OF 6 SCISEARCH on STN

2001:815447 The Genuine Article (R) Number: 477VG. Endotoxin and cytokines alter contractile protein expression in cardiac myocytes in vivo. Patten M (Reprint); Kramer E; Bunemann J; Wenck C; Thoenes M; Wieland T; Long C. Univ Hamburg, Krankenhaus Eppendorf, Abt Kardiol, Med Klin, Martinistr 52, D-20246 Hamburg, Germany (Reprint); Univ Hamburg, Krankenhaus Eppendorf, Abt Kardiol, Med Klin, D-20246 Hamburg, Germany; Univ Hamburg, Krankenhaus Eppendorf, Inst Klin & Expt Pharmakol, D-20246 Hamburg, Germany; Denver Hlth Med Ctr, Dept Cardiol, Denver, CO 80204 USA. PFLUGERS ARCHIV-EUROPEAN JOURNAL OF PHYSIOLOGY (SEP 2001) Vol. 442, No. 6, pp. 920-927. Publisher:

SPRINGER-VERLAG. 175 FIFTH AVE, NEW YORK, NY 10010 USA. ISSN: 0031-6768.
Pub. country: Germany; USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Release of bacterial endotoxin and cytokines induce cardiac failure during sepsis. We investigated the direct effects of E. coli endotoxin (lipopolysaccharide, **LPS**) and cytokines induced by **LPS** on the cardiac myocyte gene program. For in vivo-experiments adult Wistar rats were given 600 mug/day **LPS** i.v. for 24 h or 7 days. In addition. cultured adult rat cardiac myocytes were treated with **LPS**, interleukin-1 beta (IL-1 beta), tumour necrosis factor-alpha (TNF alpha), interferon-gamma (IFN gamma) or IL-6 for 24 h. mRNA expression was evaluated for cardiac-alpha -actin (cAct), skeletal-alpha -actin (skAct), beta- and alpha -myosin heavy chain (MHC). **LPS** induced beta MHC-mRNA 3.6-fold and repressed alpha MHC 2.7-fold and cAct 2.5-fold after 24 h in vivo. Up-regulation of beta MHC (3-fold) and repression of cAct (2.5-fold) were still observed after 7 days **LPS** infusion. whereas alpha MHC-mRNA levels had returned to normal. At the protein level. increased expression of beta MHC by **LPS** **treatment** occurred already after 24 h and was maintained thereafter. **LPS** had no influence on skAct-mRNA. Similar changes in contractile protein mRNA expression were observed in **LPS** -treated cardiomyocytes in culture, whereas the tested cytokines either activated (IL-1 beta, IFN gamma) or repressed (TNF alpha, IL-6) both MHC-isoforms and cAct. In conclusion. **LPS** and proinflammatory cytokines induce changes in contractile protein expression that may contribute to the acute heart failure observed during endotoxaemia.

L10 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
2000:608753 Document No. 133:193275 Preparation of phosphoric acid derivatives as TNF-α production inhibitors. Matsui, Toshiaki; Ohmawari, Nagashige (Ono Pharmaceutical Co., Ltd., Japan). PCT Int. Appl. WO 2000050429 A1 20000831, 253 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP1005 20000222. PRIORITY: JP 1999-44840 19990223; JP 1999-283104 19991004.

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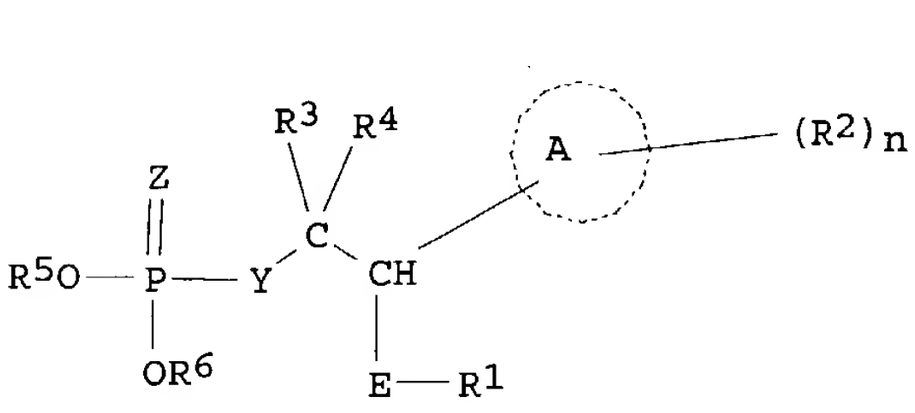

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AB The title compds. I [R1 = alkyl, etc.; ring A = heterocyclic ring, etc.; R2 = NR7CO, etc.; R7 = H, alkyl; R3, R4 = H, alkyl, etc.; further details on R3 and R4 are given; n = 0 or n ≥ 1; R5, R6 = H, alkyl, Ph, etc.; E = NR7CO, etc.; Y, Z = O, S; provisos are given] are prepared I are useful as preventives and/or remedies for rheumatoid arthritis, ulcerative colitis, Crohn's disease, hepatitis, sepsis, hemorrhagic shock, multiple sclerosis, brain infarction, diabetes, interstitial pneumonia, uveitis, pain, glomerulonephritis, HIV-associated diseases, cachexia, myocardial infarction, **chronic heart failure**, Hansen's disease, infection, etc. (2R)-2-Phenyl-2-(N-octanoylamino)ethyl phosphate

disodium salt showed ED50 of 2.6 mg/kg against TNF-α production in mice treated with **LPS.** A formulation is given.

L10 ANSWER 6 OF 6 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:437776 The Genuine Article (R) Number: 202TG. Endotoxin and immune activation in **chronic heart failure**: a prospective cohort study. Niebauer J; Volk H D; Kemp M; Dominguez M; Schumann R R; Rauchhaus M; PooleWilson P A; Coats A J S; Anker S D (Reprint). NATL HEART & LUNG INST, IMPERIAL COLL SCH MED, DOVEHOUSE ST, LONDON SW3 6LY, ENGLAND (Reprint); NATL HEART & LUNG INST, IMPERIAL COLL SCH MED, LONDON SW3 6LY, ENGLAND; UNIV LEIPZIG, HERZZENTRUM, LEIPZIG, GERMANY; UNIV KLINIKUM CHARITE, INST MED IMMUNOL, BERLIN, GERMANY; HAREFIELD HOSP, HEART SCI CTR, HAREFIELD, MIDDX, ENGLAND; UNIV KLINIKUM CHARITE, INST MIKROBIOL & HYG, BERLIN, GERMANY; MAX DELBRUCK CTR MOL MED, FRANZ VOLHARD KLIN, BERLIN, GERMANY. LANCET (29 MAY 1999) Vol. 353, No. 9167, pp. 1838-1842. Publisher: LANCET LTD. 42 BEDFORD SQUARE, LONDON WC1B 3SL, ENGLAND. ISSN: 0140-6736. Pub. country: ENGLAND; GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background. Immune activation in patients with **chronic heart failure** may be secondary to endotoxin (lipopolysaccharide) action. We investigated the hypothesis that altered gut permeability with bacterial translocation and endotoxaemia would be increased in patients with oedema secondary to congestive heart failure.

Methods. We compared 20 patients who had **chronic heart failure** with recent-onset peripheral oedema (mean age 64 years [SD 10], New York Heart Association [NYHA] class 3.3 [0.7]), 20 stable non-oedematous patients with **chronic heart failure** (mean age 63 years [19], NYHA class 2.6 [0.7]), and 14 healthy volunteers (mean age 55 years [16]). Biochemical markers of endotoxaemia, inflammation, and immune activation were measured. Ten patients were studied within 1 week of complete resolution of oedema. Five patients survived longer than 6 months and were restudied again after remaining free of oedema for more than 3 months.

Findings. Mean endotoxin concentrations were higher in oedematous patients with **chronic heart failure** than in stable patients with **chronic heart failure** (0.74 [SD 0.45] vs 0.37 EU/mL [0.23], p = 0.0009) and controls (0.46 EU/mL [0.21], p = 0.02). Oedematous patients had the highest concentrations of several cytokines. After short-term diuretic **treatment**, endotoxin concentrations decreased from 0.84 EU/mL [0.49] to 0.45 EU/mL [0.21], p < 0.05) but cytokines remained raised. After freedom of oedema for more than 3 months after oedema resolved, endotoxin concentrations remained unchanged from the previous visit (0.49 EU/mL [0.06], p = 0.45).

Interpretation. Raised concentrations of endotoxin and cytokines are found in patients with **chronic heart failure** during acute oedematous exacerbation. Intensified diuretic **treatment** can normalise endotoxin concentrations. Our preliminary findings suggest that endotoxin may trigger immune activation in patients with **chronic heart failure** during oedematous episodes.

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2003:47605   The Genuine Article (R) Number: 630BL. Taurine modulates induction
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of cytochrome P450 3A4 mRNA by rifampicin in the HepG2 cell line. Matsuda H; Kinoshita K; Sumida A; Takahashi K; Fukuen S; Fukuda T; Takahashi K; Yamamoto I; Azuma J (Reprint). Osaka Univ, Grad Sch Pharmaceut Sci, 1-6 Yamadaoka, Suita, Osaka 5650871, Japan (Reprint); Osaka Univ, Grad Sch Pharmaceut Sci, Suita, Osaka 5650871, Japan; Mukogawa Womens Univ, Sch Pharmaceut Sci, Dept Pharmaceut, Nishinomiya, Hyogo, Japan. BIOCHIMICA ET BIOPHYSICA ACTA-MOLECULAR CELL RESEARCH (16 DEC 2002) Vol. 1593, No. 1, pp. 93-98. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0167-4889. Pub. country: Japan. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Taurine is not only present in foods, tonics and nutrient drinks but is also used as a medicinal agent mainly for treatment of **chronic heart failure** and liver disease. However, little is known about its influence on drug-metabolizing enzymes, especially cytochrome P450 (CYP), in human. We examined whether. taurine could affect the expression of CYP3A4 mRNA in the presence or absence of rifampicin (RFP), which is a potent inducer of CYPs, with HepG2 cells. Taurine enhanced twice the induction of CYP3A4 mRNA by RFP, but did not affect the expression by itself. This effect was both concentration- and time-dependent. On the other hand, taurine did not affect the induction by phenobarbital. Taurine did not increase intracellular uptake of RFP. Therefore, we conclude that taurine is an enhancer for the induction of CYP3A4 by RFP. (C) 2002 Elsevier Science B.V. All rights reserved.

L12 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN

2000:645885 Document No. 133:217694 Endotoxin-modulating compounds for therapy of heart failure and cachexia. Anker, Stefan; Coats, Andrew; Volk, Hans-Dieter; Rauchhaus, Mathias; Schumann, Ralf Reiner (Max-Delbruck-Centrum fur Molekulare Medizin, Germany). PCT Int. Appl. WO 2000053224 A2 20000914, 74 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP2299 20000309. PRIORITY: GB 1999-5300 19990309; GB 1999-5307 19990309; GB 1999-5310 19990309; GB 1999-5314 19990309; GB 1999-5315 19990309.

AB A method of treating, preventing or ameliorating chronic or acute heart failure in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, **bile acids**, or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a **bile acid** or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. A method of treating, preventing or ameliorating endotoxin-mediated immune activation in acute or **chronic heart failure** in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, **bile acids** or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a **bile acid** or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. Also disclosed is a method for treating cachexia and wasting syndromes due to

diseases other than congestive heart failure.

```
=> s l1 and ursodesoxycholic acid
L13             0 L1 AND URSODESOXYCHOLIC ACID

=> s ursodesoxycholic acid
L14           236 URSODESOXYCHOLIC ACID

=> s l14 and LPS
L15             0 L14 AND LPS

=> s l14 and TNF
L16             1 L14 AND TNF

=> d l16 cbib abs

L16  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2004 ACS on STN
1994:95769   Document No. 120:95769  Tumor necrosis factor (TNF)
     formation enhancers.  Sekido, Shosaburo (Tokyo Tanabe Co, Japan).  Jpn.
     Kokai Tokkyo Koho JP 05279259 A2 19931026 Heisei, 6 pp.  (Japanese).
     CODEN: JKXXAF.  APPLICATION: JP 1991-133793 19910330.
AB   TNF formation enhancers, useful for treatment of cancer, contain
     ursodesoxycholic acid (I) or its pharmacol. acceptable
     salts as active active ingredient(s).  I at 10 μg/mL remarkably
     increased TNF formation in THP1 cells and at 120 mg/kg i.p.
     strongly suppressed tumor growth in mice.


=> s chemodeoxycholic acid and TNF
L17             0 CHEMODEOXYCHOLIC ACID AND TNF

=> s chemodeoxycholic acid
L18            33 CHEMODEOXYCHOLIC ACID

=> s l18 and LPS
L19             0 L18 AND LPS

=> s l18 and inflamatory cytokine
L20             0 L18 AND INFLAMATORY CYTOKINE

=> dup remove l18
PROCESSING COMPLETED FOR L18
L21            33 DUP REMOVE L18 (0 DUPLICATES REMOVED)

=> d l18 and chronic heart failure
'AND' IS NOT A VALID FORMAT
'CHRONIC' IS NOT A VALID FORMAT
'HEART' IS NOT A VALID FORMAT
'FAILURE' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
in at least one of the files.  Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):d l21
'D' IS NOT A VALID FORMAT
'L111' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
in at least one of the files.  Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT): d l21 cbib abs
'D' IS NOT A VALID FORMAT
'L111' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
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in at least one of the files. Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):d
'D' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
in at least one of the files. Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):d cbib abs
'D' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
in at least one of the files. Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):s chemo
'S' IS NOT A VALID FORMAT
'CHEMO' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
in at least one of the files. Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):

---Logging off of STN---

REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):END

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	95.80	96.01

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.08	-2.08

STN INTERNATIONAL LOGOFF AT 16:17:26 ON 15 JUN 2004

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1644PNH

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
NEWS	4	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
NEWS	5	FEB 05	German (DE) application and patent publication number format changes
NEWS	6	MAR 03	MEDLINE and LMEDLINE reloaded
NEWS	7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS	8	MAR 03	FRANCEPAT now available on STN
NEWS	9	MAR 29	Pharmaceutical Substances (PS) now available on STN
NEWS	10	MAR 29	WPIFV now available on STN
NEWS	11	MAR 29	New monthly current-awareness alert (SDI) frequency in RAPRA
NEWS	12	APR 26	PROMT: New display field available
NEWS	13	APR 26	IFIPAT/IFIUDB/IFICDB: New super search and display field available
NEWS	14	APR 26	LITALERT now available on STN
NEWS	15	APR 27	NLDB: New search and display fields available
NEWS	16	May 10	PROUSDDR now available on STN
NEWS	17	May 19	PROUSDDR: One FREE connect hour, per account, in both May and June 2004
NEWS	18	May 12	EXTEND option available in structure searching
NEWS	19	May 12	Polymer links for the POLYLINK command completed in REGISTRY
NEWS	20	May 17	FRFULL now available on STN
NEWS	21	May 27	STN User Update to be held June 7 and June 8 at the SLA 2004 Conference
NEWS	22	May 27	New UPM (Update Code Maximum) field for more efficient patent SDIs in CAplus
NEWS	23	May 27	CAplus super roles and document types searchable in REGISTRY
NEWS	24	May 27	Explore APOLLIT with free connect time in June 2004

NEWS EXPRESS	MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
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NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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FILE 'HOME' ENTERED AT 16:08:34 ON 15 JUN 2004

=> file medline embase biosis scisearch caplus
COST IN U.S. DOLLARS                                          SINCE FILE      TOTAL
                                                                 ENTRY    SESSION
FULL ESTIMATED COST                                               0.21       0.21

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=> s chronic heart failure
L1         22006 CHRONIC HEART FAILURE

=> s l1 and prevention
L2           718 L1 AND PREVENTION

=> s l2 and effective
L3            87 L2 AND EFFECTIVE

=> dup remove l3
PROCESSING COMPLETED FOR L3
L4            56 DUP REMOVE L3 (31 DUPLICATES REMOVED)

=> s l4 and LPS
L5             0 L4 AND LPS

=> s l2 and reduce LPS
L6             0 L2 AND REDUCE LPS

=> s l2 and LPS
L7             0 L2 AND LPS

=> s l1 and LPS
L8            47 L1 AND LPS

=> s l8 and treatment
L9             7 L8 AND TREATMENT

=> dup remove l9
PROCESSING COMPLETED FOR L9
L10            6 DUP REMOVE L9 (1 DUPLICATE REMOVED)

=> d l10 1-6 cbib abs

L10  ANSWER 1 OF 6     MEDLINE on STN                          DUPLICATE 1
2004283437.    PubMed ID: 15182775.   Selective intestinal decontamination in
     advanced chronic heart failure: a pilot
     trial. Conraads Viviane M; Jorens Philippe G; De Clerck Luc S; Van Saene
     Hendrik K; Ieven Margaretha M; Bosmans Johan M; Schuerwegh Annemie; Bridts
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Chris H; Wuyts Floris; Stevens Wim J; Anker Stefan D; Rauchhaus Mathias; Vrints Christiaan J. (Department of Cardiology, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium.) European journal of heart failure : journal of the Working Group on Heart Failure of the European Society of Cardiology, (2004 Jun) 6 (4) 483-91. Journal code: 100887595. ISSN: 1388-9842. Pub. country: Netherlands. Language: English.

AB Background and aims: Endotoxin, derived from intestinal aerobic Gram-negative bacilli (AGNB), could be an important monocyte activator in **chronic heart failure** (CHF). The effect of selective decontamination of the digestive tract (SDD) on intracellular monocyte cytokine production, monocyte CD14 expression, circulating endotoxin and cytokines, and flow-mediated dilation (FMD) was studied in patients with severe CHF. Methods and results: Ten patients with CHF (NYHA class III-IV) were enrolled in a non-placebo controlled pilot trial involving the administration of SDD (polymyxin B, tobramycin) for 8 weeks. One patient was later excluded due to cardiac transplantation. Before **treatment**, after 4 and 8 weeks therapy, and 6 weeks post-**treatment**, monocyte CD14 expression, intracellular monocyte production of interleukin-1beta [IL-1beta], interleukin-6 [IL-6], tumour necrosis factor (TNF)-alpha with and without lipopolysaccharide (**LPS**) stimulation were measured. Concentrations of endotoxin and cytokines (IL-1beta, IL-6, TNF-alpha) were also determined. AGNB in faeces, intestinal endotoxin and FMD were assessed at baseline, after 4 weeks of **treatment** and 6 weeks post-**treatment.** SDD eradicated intestinal AGNB (P<0.00001) and decreased faecal endotoxin concentrations (P<0.00001). There was a significant decline in monocyte CD14 expression (P=0.03) and in IL-1beta (P=0.0001), IL-6 (P=0.02) and TNF-alpha (P=0.0002) production after 4 and 8 weeks of **treatment** in the basal state and for IL-1beta (P=0.008) and IL-6 (P=0.005) after **LPS** stimulation. FMD significantly improved at 4 weeks and returned to baseline after **treatment** discontinuation (P=0.002). Circulating concentrations of endotoxin and cytokines remained unchanged. Conclusion: Reduction of the intestinal endotoxin pool led to a decrease in monocyte CD14 expression and intracellular cytokine production in patients with severe CHF. The improvement of peripheral endothelial function could be a marker of the anti-inflammatory effect of SDD.

L10 ANSWER 2 OF 6 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2003:576101 The Genuine Article (R) Number: 697RP. Myocardial IL-6 regulation by neurohormones - an in vitro superfusion study. Jeron A (Reprint); Kaiser T; Straub R H; Weil J; Riegger G A J; Muders F. Klinikum Univ Regensburg, Klin & Poliklin Innere Med 2, Franz Josef Strauss Allee 11, D-93042 Regensburg, Germany (Reprint); Klinikum Univ Regensburg, Klin & Poliklin Innere Med 2, D-93042 Regensburg, Germany; Klinikum Univ Regensburg, Klin & Poliklin Innere Med 1, D-93042 Regensburg, Germany. BRAIN BEHAVIOR AND IMMUNITY (AUG 2003) Vol. 17, No. 4, pp. 245-250. Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA. ISSN: 0889-1591. Pub. country: Germany. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Interleukin-6 (IL-6) is expressed in the myocardium and has been implicated in cell proliferation, negative inotropic effects and myocardial hypertrophy. To determine whether myocardial IL-6 is modified by neuro-humoral and immunoregulatory stimuli, we studied the effects of lipopolysaccharide (**LPS**), corticosterone (CS), isoproterenol and angiotensin II on myocardial IL-6 secretion in superfused myocardium.

Methods: Slices of rat left ventricular myocardium were superfused in 80 mul chambers for up to 5 h. **LPS** (1, 50, and 100 mug/ml), CS (10(-7), 10(-6), and 10(-5) M, DSMO as vehicle), isoproterenol (10(-6), 10(-7), and 10(-8) M) and angiotensin II (10(-5), 10(-7), and 10(-9) M) were added to the culture medium at hour 2. IL-6 was measured in the perfusate by ELISA.

Results: Physiological corticosterone concentrations (10(-7) M) resulted in an increase in IL-6 concentration (142%) while high doses of steroid decreased IL-6 significantly (CS 10(-6) M: 88 +/- 14%, p <.05; CS

10(-5): 91 +/- 9%, p < .05) after 5 h. Left ventricular IL-6 secretion was significantly stimulated by **LPS** 50 mug/ml (3262 1684% vs. CTRL: 116 +/- 134%, p < .01). Isoproterenol **treatment** increased in IL-6 secretion compared to controls with and without CS, while angiotensin II reduced IL-6 concentration only in combination with CS.

Conclusion: Myocardial IL-6 secretion is modulated by physiological concentrations of corticosterone or angiotensin II and can be induced by **LPS** or isoproterenol, indicating a tight regulation of this cytokine. Suppression of cytokine expression within the heart might be a potential therapeutic goal in the **treatment** of various cardiovascular diseases.

L10 ANSWER 3 OF 6 EMBASE
on STN

2002294975 EMBASE Effect of interleukin-10 on the production of tumor necrosis factor-alpha by peripheral blood mononuclear cells from patients with **chronic heart failure.** Bolger A.P.; Sharma R.; Von Haehling S.; Doehner W.; Oliver B.; Rauchhaus M.; Coats A.J.S.; Adcock I.M.; Anker S.D.. A.P. Bolger, Department of Clinical Cardiology, National Heart and Lung Institute, London SW3 6LY, United Kingdom. a.bolger@ic.ac.uk. American Journal of Cardiology 90/4 (384-389) 15 Aug 2002.

Refs: 29.

ISSN: 0002-9149. CODEN: AJCDAG.
Publisher Ident.: S 0002-9149(02)02494-3. Pub. Country: United States.
Language: English. Summary Language: English.

AB **Chronic heart failure** (HF) is a state of inflammatory immune activation characterized by elevated circulating levels of tumor necrosis factor-α (TNF-α). Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine that inhibits TNF-α production and lessens endotoxin bioactivity. It is not known whether IL-10 reduces lipopolysaccharide (**LPS**) stimulated TNF-α production of peripheral blood mononuclear cells (PBMCs) from patients with chronic HF. PBMCs were isolated from 15 patients with chronic HF (New York Heart Association functional class 3.0 ± 0.2, left ventricular ejection fraction 30 ± 2%, peak oxygen consumption 18.1 ± 0.8 ml/kg/min) and 15 healthy control subjects and stimulated with 1 and 10 ng/ml **LPS** for 24 hours with or without prior addition of IL-10 (10 ng/ml). TNF-α was quantified in cell-free supernatants by an enzyme-linked immunosorbent assay. TNF-α, soluble TNF receptors, IL-10, and **LPS** were quantified in plasma. **LPS** stimulated TNF-α production was highest in those patients in New York Heart Association class II (p <0.01 vs New York Heart Association class III and IV, p <0.001 vs control subjects). IL-10 reduced PBMC TNF-α production in all stimulated samples at 1 and 10 ng/ml **LPS** (mean reduction 43% at 1 ng/ml, p <0.01 and 55% at 10 ng/ml, p <0.0001). The percentage reduction in TNF-α release did not differ significantly between patients and control subjects or with respect to severity of chronic HF or baseline immune parameters. Independently of clinical severity, IL-10 profoundly inhibits TNF-α release from PBMCs isolated from patients with chronic HF. IL-10 is, therefore, a potential therapy for use in chronic HF associated with inflammatory immune activation.

L10 ANSWER 4 OF 6 SCISEARCH on STN

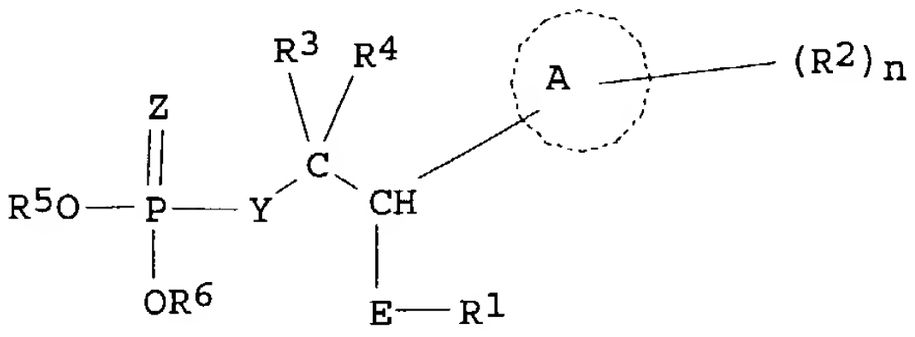
2001:815447 The Genuine Article (R) Number: 477VG. Endotoxin and cytokines alter contractile protein expression in cardiac myocytes in vivo. Patten M (Reprint); Kramer E; Bunemann J; Wenck C; Thoenes M; Wieland T; Long C. Univ Hamburg, Krankenhaus Eppendorf, Abt Kardiol, Med Klin, Martinistr 52, D-20246 Hamburg, Germany (Reprint); Univ Hamburg, Krankenhaus Eppendorf, Abt Kardiol, Med Klin, D-20246 Hamburg, Germany; Univ Hamburg, Krankenhaus Eppendorf, Inst Klin & Expt Pharmakol, D-20246 Hamburg, Germany; Denver Hlth Med Ctr, Dept Cardiol, Denver, CO 80204 USA. PFLUGERS ARCHIV-EUROPEAN JOURNAL OF PHYSIOLOGY (SEP 2001) Vol. 442, No. 6, pp. 920-927. Publisher:

SPRINGER-VERLAG. 175 FIFTH AVE, NEW YORK, NY 10010 USA. ISSN: 0031-6768.
Pub. country: Germany; USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Release of bacterial endotoxin and cytokines induce cardiac failure during sepsis. We investigated the direct effects of E. coli endotoxin (lipopolysaccharide, **LPS**) and cytokines induced by **LPS** on the cardiac myocyte gene program. For in vivo-experiments adult Wistar rats were given 600 mug/day **LPS** i.v. for 24 h or 7 days. In addition. cultured adult rat cardiac myocytes were treated with **LPS**, interleukin-1 beta (IL-1 beta), tumour necrosis factor-alpha (TNF alpha), interferon-gamma (IFN gamma) or IL-6 for 24 h. mRNA expression was evaluated for cardiac-alpha -actin (cAct), skeletal-alpha -actin (skAct), beta- and alpha -myosin heavy chain (MHC). **LPS** induced beta MHC-mRNA 3.6-fold and repressed alpha MHC 2.7-fold and cAct 2.5-fold after 24 h in vivo. Up-regulation of beta MHC (3-fold) and repression of cAct (2.5-fold) were still observed after 7 days **LPS** infusion. whereas alpha MHC-mRNA levels had returned to normal. At the protein level. increased expression of beta MHC by **LPS** **treatment** occurred already after 24 h and was maintained thereafter. **LPS** had no influence on skAct-mRNA. Similar changes in contractile protein mRNA expression were observed in **LPS** -treated cardiomyocytes in culture, whereas the tested cytokines either activated (IL-1 beta, IFN gamma) or repressed (TNF alpha, IL-6) both MHC-isoforms and cAct. In conclusion. **LPS** and proinflammatory cytokines induce changes in contractile protein expression that may contribute to the acute heart failure observed during endotoxaemia.

L10 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
2000:608753 Document No. 133:193275 Preparation of phosphoric acid derivatives as TNF-α production inhibitors. Matsui, Toshiaki; Ohmawari, Nagashige (Ono Pharmaceutical Co., Ltd., Japan). PCT Int. Appl. WO 2000050429 A1 20000831, 253 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP1005 20000222. PRIORITY: JP 1999-44840 19990223; JP 1999-283104 19991004.

GI



I

AB The title compds. I [R1 = alkyl, etc.; ring A = heterocyclic ring, etc.; R2 = NR7CO, etc.; R7 = H, alkyl; R3, R4 = H, alkyl, etc.; further details on R3 and R4 are given; n = 0 or n ≥ 1; R5, R6 = H, alkyl, Ph, etc.; E = NR7CO, etc.; Y, Z = O, S; provisos are given] are prepared I are useful as preventives and/or remedies for rheumatoid arthritis, ulcerative colitis, Crohn's disease, hepatitis, sepsis, hemorrhagic shock, multiple sclerosis, brain infarction, diabetes, interstitial pneumonia, uveitis, pain, glomerulonephritis, HIV-associated diseases, cachexia, myocardial infarction, **chronic heart failure**, Hansen's disease, infection, etc. (2R)-2-Phenyl-2-(N-octanoylamino)ethyl phosphate

disodium salt showed ED50 of 2.6 mg/kg against TNF-α production in mice treated with **LPS.** A formulation is given.

L10 ANSWER 6 OF 6 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:437776 The Genuine Article (R) Number: 202TG. Endotoxin and immune activation in **chronic heart failure**: a prospective cohort study. Niebauer J; Volk H D; Kemp M; Dominguez M; Schumann R R; Rauchhaus M; PooleWilson P A; Coats A J S; Anker S D (Reprint). NATL HEART & LUNG INST, IMPERIAL COLL SCH MED, DOVEHOUSE ST, LONDON SW3 6LY, ENGLAND (Reprint); NATL HEART & LUNG INST, IMPERIAL COLL SCH MED, LONDON SW3 6LY, ENGLAND; UNIV LEIPZIG, HERZZENTRUM, LEIPZIG, GERMANY; UNIV KLINIKUM CHARITE, INST MED IMMUNOL, BERLIN, GERMANY; HAREFIELD HOSP, HEART SCI CTR, HAREFIELD, MIDDX, ENGLAND; UNIV KLINIKUM CHARITE, INST MIKROBIOL & HYG, BERLIN, GERMANY; MAX DELBRUCK CTR MOL MED, FRANZ VOLHARD KLIN, BERLIN, GERMANY. LANCET (29 MAY 1999) Vol. 353, No. 9167, pp. 1838-1842. Publisher: LANCET LTD. 42 BEDFORD SQUARE, LONDON WC1B 3SL, ENGLAND. ISSN: 0140-6736. Pub. country: ENGLAND; GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background. Immune activation in patients with **chronic heart failure** may be secondary to endotoxin (lipopolysaccharide) action. We investigated the hypothesis that altered gut permeability with bacterial translocation and endotoxaemia would be increased in patients with oedema secondary to congestive heart failure.

Methods. We compared 20 patients who had **chronic heart failure** with recent-onset peripheral oedema (mean age 64 years [SD 10], New York Heart Association [NYHA] class 3.3 [0.7]), 20 stable non-oedematous patients with **chronic heart failure** (mean age 63 years [19], NYHA class 2.6 [0.7]), and 14 healthy volunteers (mean age 55 years [16]). Biochemical markers of endotoxaemia, inflammation, and immune activation were measured. Ten patients were studied within 1 week of complete resolution of oedema. Five patients survived longer than 6 months and were restudied again after remaining free of oedema for more than 3 months.

Findings. Mean endotoxin concentrations were higher in oedematous patients with **chronic heart failure** than in stable patients with **chronic heart failure** (0.74 [SD 0.45] vs 0.37 EU/mL [0.23], p = 0.0009) and controls (0.46 EU/mL [0.21], p = 0.02). Oedematous patients had the highest concentrations of several cytokines. After short-term diuretic **treatment**, endotoxin concentrations decreased from 0.84 EU/mL [0.49] to 0.45 EU/mL [0.21], p < 0.05) but cytokines remained raised. After freedom of oedema for more than 3 months after oedema resolved, endotoxin concentrations remained unchanged from the previous visit (0.49 EU/mL [0.06], p = 0.45).

Interpretation. Raised concentrations of endotoxin and cytokines are found in patients with **chronic heart failure** during acute oedematous exacerbation. Intensified diuretic **treatment** can normalise endotoxin concentrations. Our preliminary findings suggest that endotoxin may trigger immune activation in patients with **chronic heart failure** during oedematous episodes.

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=> s l1 and bile acid
   3 FILES SEARCHED...
L11           2 L1 AND BILE ACID

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PROCESSING COMPLETED FOR L11
L12            2 DUP REMOVE L11 (0 DUPLICATES REMOVED)

=> d l12 1-2 cbib abs

L12  ANSWER 1 OF 2  SCISEARCH  COPYRIGHT 2004 THOMSON ISI on STN
2003:47605  The Genuine Article (R) Number: 630BL. Taurine modulates induction
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of cytochrome P450 3A4 mRNA by rifampicin in the HepG2 cell line. Matsuda H; Kinoshita K; Sumida A; Takahashi K; Fukuen S; Fukuda T; Takahashi K; Yamamoto I; Azuma J (Reprint). Osaka Univ, Grad Sch Pharmaceut Sci, 1-6 Yamadaoka, Suita, Osaka 5650871, Japan (Reprint); Osaka Univ, Grad Sch Pharmaceut Sci, Suita, Osaka 5650871, Japan; Mukogawa Womens Univ, Sch Pharmaceut Sci, Dept Pharmaceut, Nishinomiya, Hyogo, Japan. BIOCHIMICA ET BIOPHYSICA ACTA-MOLECULAR CELL RESEARCH (16 DEC 2002) Vol. 1593, No. 1, pp. 93-98. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0167-4889. Pub. country: Japan. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Taurine is not only present in foods, tonics and nutrient drinks but is also used as a medicinal agent mainly for treatment of **chronic heart failure** and liver disease. However, little is known about its influence on drug-metabolizing enzymes, especially cytochrome P450 (CYP), in human. We examined whether. taurine could affect the expression of CYP3A4 mRNA in the presence or absence of rifampicin (RFP), which is a potent inducer of CYPs, with HepG2 cells. Taurine enhanced twice the induction of CYP3A4 mRNA by RFP, but did not affect the expression by itself. This effect was both concentration- and time-dependent. On the other hand, taurine did not affect the induction by phenobarbital. Taurine did not increase intracellular uptake of RFP. Therefore, we conclude that taurine is an enhancer for the induction of CYP3A4 by RFP. (C) 2002 Elsevier Science B.V. All rights reserved.

L12 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN

2000:645885 Document No. 133:217694 Endotoxin-modulating compounds for therapy of heart failure and cachexia. Anker, Stefan; Coats, Andrew; Volk, Hans-Dieter; Rauchhaus, Mathias; Schumann, Ralf Reiner (Max-Delbruck-Centrum fur Molekulare Medizin, Germany). PCT Int. Appl. WO 2000053224 A2 20000914, 74 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP2299 20000309. PRIORITY: GB 1999-5300 19990309; GB 1999-5307 19990309; GB 1999-5310 19990309; GB 1999-5314 19990309; GB 1999-5315 19990309.

AB A method of treating, preventing or ameliorating chronic or acute heart failure in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, **bile acids**, or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a **bile acid** or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. A method of treating, preventing or ameliorating endotoxin-mediated immune activation in acute or **chronic heart failure** in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, **bile acids** or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a **bile acid** or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. Also disclosed is a method for treating cachexia and wasting syndromes due to

diseases other than congestive heart failure.

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=> s l1 and ursodesoxycholic acid
L13             0 L1 AND URSODESOXYCHOLIC ACID

=> s ursodesoxycholic acid
L14           236 URSODESOXYCHOLIC ACID

=> s l14 and LPS
L15             0 L14 AND LPS

=> s l14 and TNF
L16             1 L14 AND TNF

=> d l16 cbib abs

L16  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2004 ACS on STN
1994:95769   Document No. 120:95769  Tumor necrosis factor (TNF)
     formation enhancers.  Sekido, Shosaburo (Tokyo Tanabe Co, Japan).  Jpn.
     Kokai Tokkyo Koho JP 05279259 A2 19931026 Heisei, 6 pp.  (Japanese).
     CODEN: JKXXAF.  APPLICATION: JP 1991-133793 19910330.
AB   TNF formation enhancers, useful for treatment of cancer, contain
     ursodesoxycholic acid (I) or its pharmacol. acceptable
     salts as active active ingredient(s).  I at 10 μg/mL remarkably
     increased TNF formation in THP1 cells and at 120 mg/kg i.p.
     strongly suppressed tumor growth in mice.


=> s chemodeoxycholic acid and TNF
L17             0 CHEMODEOXYCHOLIC ACID AND TNF

=> s chemodeoxycholic acid
L18            33 CHEMODEOXYCHOLIC ACID

=> s l18 and LPS
L19             0 L18 AND LPS

=> s l18 and inflamatory cytokine
L20             0 L18 AND INFLAMATORY CYTOKINE

=> dup remove l18
PROCESSING COMPLETED FOR L18
L21            33 DUP REMOVE L18 (0 DUPLICATES REMOVED)

=> d l18 and chronic heart failure
'AND' IS NOT A VALID FORMAT
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'HEART' IS NOT A VALID FORMAT
'FAILURE' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
in at least one of the files.  Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):d l21
'D' IS NOT A VALID FORMAT
'L111' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
in at least one of the files.  Refer to file specific help messages
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individual files.
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'D' IS NOT A VALID FORMAT
'L111' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
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in at least one of the files.  Refer to file specific help messages
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individual files.
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in at least one of the files.  Refer to file specific help messages
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REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):s chemo
'S' IS NOT A VALID FORMAT
'CHEMO' IS NOT A VALID FORMAT
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                                                      ENTRY     SESSION
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                   and searchable
 NEWS  4  JAN 27   A new search aid, the Company Name Thesaurus, available in
                   CA/CAplus
 NEWS  5  FEB 05   German (DE) application and patent publication number format
                   changes
 NEWS  6  MAR 03   MEDLINE and LMEDLINE reloaded
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 NEWS 12  APR 26   PROMT: New display field available
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                   available
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 NEWS 15  APR 27   NLDB: New search and display fields available
 NEWS 16  May 10   PROUSDDR now available on STN
 NEWS 17  May 19   PROUSDDR: One FREE connect hour, per account, in both May
                   and June 2004
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 NEWS 19  May 12   Polymer links for the POLYLINK command completed in REGISTRY
 NEWS 20  May 17   FRFULL now available on STN
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                   Conference
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                                                         ENTRY    SESSION
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=> s cheodeoxycholic acid
L1 1 CHEODEOXYCHOLIC ACID

=> d l1 cbib abs

L1 ANSWER 1 OF 1 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
84072610 EMBASE Document No.: 1984072610. Experience with a long-term application of **cheodeoxycholic acid** to the treatment of patients with cholelithiasis. Mansurov Kh.Kh.; Mansurova Kh. F.. Tadzhikskij Institut Gastroenterologii, Dushanbe, Russia. Terapevticheskii Arkhiv 56/1 (43-47) 1984.
CODEN: TEARAI. Pub. Country: Russia. Language: Russian. Summary Language: English.

=> s chemodeoxycholic acid
L2 33 CHEMODEOXYCHOLIC ACID

=> s l2 and treatment
L3 13 L2 AND TREATMENT

=> dup remove l3
PROCESSING COMPLETED FOR L3
L4 13 DUP REMOVE L3 (0 DUPLICATES REMOVED)

=> d l4 1-13 cbib abs

L4 ANSWER 1 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
97117362 EMBASE Document No.: 1997117362. Failure in the **treatment** of long-standing osteoporosis in cerebrotendinous xanthomatosis. Chang W.-N.; Lui C.-C.. Dr. W.-N. Chang, Department of Neurology, Chang Gung Memorial Hospital, 123 Ta Pei Road, Niao Sung Hsiang, Kaohsiung Hsien, Taiwan,Province of China. Journal of the Formosan Medical Association 96/3 (225-227) 1997.
Refs: 15.
ISSN: 0929-6646. CODEN: JFASEO. Pub. Country: Taiwan,Province of China.
Language: English. Summary Language: English.

AB We evaluated the therapeutic effect of combined therapy with **chemodeoxycholic acid**, calcium carbonate, and sodium bicarbonate on long-standing osteoporosis in three siblings (two women and one man, aged 30-38 yrs) with cerebrotendinous xanthomatosis (CTX). The evaluation was based on the measurement of bone mineral density (BMD) before and after 3 years of combined therapy. Clinically, the therapeutic effect was quite limited (almost no change in BMD values), and did not parallel the marked decrease in serum cholestanol level (normalization of serum levels). While the reason for the therapeutic failure in our patients is not known, it is possible that delay in starting **treatment** may have been a factor. Measurement of BMD for evaluation of therapeutic effect in long-standing osteoporosis in CTX patients is of little practical value.

L4 ANSWER 2 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

96179875 EMBASE Document No.: 1996179875. Effects of β-lactam antibiotics on intestinal microflora and bile acid metabolism in rats. Hashimoto S.; Igimi H.; Uchida K.; Satoh T.; Benno Y.; Takeuchi N.. Strategic Information Unit, Shionogi and Co., Ltd.,Shibuya-ku, Tokyo 150, Japan. Lipids 31/6 (601-609) 1996.
ISSN: 0024-4201. CODEN: LPDSAP. Pub. Country: United States. Language: English. Summary Language: English.

AB Wistar male rats were treated for six days with broad spectrum β-lactam antibiotics, latamoxef, and cefotaxime. On the seventh day, the number of fecal anaerobic microbes decreased, total fecal bile acids decreased, and bile acid pools increased. Secondary bile acids such as β-hyocholic, hyodeoxycholic, lithocholic, and deoxycholic acids decreased in the feces while the primary bile acids, cholic, β-muricholic, and **chemodeoxycholic acids**, became predominant. Coprostanol, a microbial metabolite of cholesterol, also disappeared from the fetes during the **treatment.** The cecum enlarged to almost twice the size of that in control rats, whereas the liver weight was not significantly changed. After **treatment** was stopped, the number of fecal microbes returned to the initial counts within a week, but restoration of bile acid and cholesterol metabolism required at least three weeks.

L4 ANSWER 3 OF 13 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

92:596269 The Genuine Article (R) Number: JR380. **TREATMENT** OF ERYTHROPOIETIC PROTOPORPHYRIA (EPP) WITH **CHEMODEOXYCHOLIC ACID** AND URSODEOXYCHOLIC ACID - LIGHT-INDUCED TOLERANCE. VANWEELDEN H (Reprint); VANHATTUM J; BIJLMERIEST J; DELAFAILLE H B. UNIV UTRECHT HOSP, DEPT DERMATOL & HEPATOGASTROENTEROL, 3511 GV UTRECHT, NETHERLANDS. HEPATOLOGY (OCT 1992) Vol. 16, No. 4, Part 2, pp. A238. ISSN: 0270-9139. Pub. country: NETHERLANDS. Language: ENGLISH.

L4 ANSWER 4 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

1992:120294 Document No.: PREV199293066094; BA93:66094. THE EFFECT OF BILE ACIDS ON THE GROWTH AND ADHERENCE OF HELICOBACTER-PYLORI. MATHAI E [Reprint author]; ARORA A; CAFFERKEY M; KEANE C T; O'MORAIN C. DEP CLIN MICROBIOL, TRINITY COLL, ST JAMES'S HOSP, DUBLIN 8, EIRE. Alimentary Pharmacology and Therapeutics, (1991) Vol. 5, No. 6, pp. 653-658.
CODEN: APTHEN. ISSN: 0269-2813. Language: ENGLISH.

AB Bile reflux gastritis occurs in the absence of Helicobacter pylori (H. pylori). The aim of this study was to see if the bile acids cheno or ursodeoxycholic acid affected the growth or adherence of H. pylori in vitro. Twenty-seven strains growth were inhibited by 0.1% chenodeoxycholic acid whereas only 11 out of the 27 were inhibited by 0.1% ursodeoxycholic acid. Growth was totally inhibited by a combination of 0.05% **chemodeoxycholic acid** + 0.05% ursodeoxycholic combination of 0.05% chenodeoxycholic acid. Chenodeoxycholic acid was a more effective inhibitor of adherence in that the number inhibited and percentage inhibition were greater than with ursodeoxycholic acid. Bile salts might be useful in the **treatment** of H. pylori infection.

L4 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

1990:526615 Document No. 113:126615 Chenodeoxycholic acid and swine bile as antihypertensives. Katsuta, Shinichiro; Oji, Shiro (Nippon Meat Packers, Inc., Japan). Jpn. Kokai Tokkyo Koho JP 02025425 A2 19900126 Heisei, 5 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1988-175922 19880713.

AB Chenodeoxycholic acid or swine bile (with/without **treatment** to remove low mol.-weight substances) is effective in treating hypertension. Antihypertensive activity of these substances was demonstrated in dogs. The prepns. are as effective as hydrolazine-HCl but have min. side effects.

L4 ANSWER 6 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN
88078319 EMBASE Document No.: 1988078319. Psychiatric disorders in patients with cerebrotendinous xanthomatosis. Berginer V.M.; Foster N.L.; Sadowsky M.; Townsend III J.A.; Siegel G.J.; Salen G.. Department of Neurology, Soroka Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel. American Journal of Psychiatry 145/3 (354-357) 1988.
ISSN: 0002-953X. CODEN: AJPSAO. Pub. Country: United States. Language: English. Summary Language: English.

AB Cerebrotendinous xanthomatosis is a familial recessive disorder. Patients with the disorder present with tendon xanthomas, juvenile cataracts, dementia, and pyramidal and cerebellar abnormalities but have normal phase cholesterol. High plasma cholestanol concentrations and abnormal bile acid metabolism are specific for this disease. The authors describe four patients with cerebrotendinous xanthomatosis and prominent psychiatric symptoms. In three of these patients appropriate diagnosis and **treatment** were delayed for years because the presence of cerebrotendinous xanthomatosis was not recognized. Early recognition of this potentially lethal disease is important because both the psychiatric and neurological symptoms respond to **treatment** with **chemodeoxycholic acid.**

L4 ANSWER 7 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1988:48288 Document No.: PREV198885025147; BA85:25147. A STUDY ON SIZE OF MOLECULAR AGGREGATES FORMED BY BILE ACID IN HUMAN GALLBLADDER BILE WITH SPECIAL REFERENCE TO COMPARISON OF CHENODEOXYCHOLIC ACID-RICH BILE AND URSODEOXYCHOLIC ACID-RICH BILE. YONEDA M [Reprint author]. THIRD DEP INTERN MED, HIROSAKI UNIV SCH MED, HIROSAKI, JPN. Hirosaki Medical Journal, (1987) Vol. 39, No. 3, pp. 414-426.
CODEN: HIRIA6. ISSN: 0439-1721. Language: JAPANESE.

AB The size of molecular aggregates (generally, micelle) formed by bile acid in human gall-bladder bile and model bile solution was studied by utilizing disposal ultrafiltration unit (cut-off molecular weight: 10,000 and 1,000). In gallbladder bile without any bile acid **treatment** (n=20), 66% of total bile acid was observed in large aggregate fraction (molecular weight : above 10,000) and 18% in small particle fraction (dimer and monomer). In **chemodeoxycholic acid**-rich bile (n=8), the large fraction was increased to 73% of total bile acid and small fraction was decreased to 13%, as compared with gallbladder bile without any bile acid **treatment.** On the other hand, in ursodeoxycholic-rich bile (n=8), large fraction was decreased to 59% while small fraction was increased to 24%. Additionally, major constituent of dimer and monomer was cholic acid or urodeoxychokic acid. Thus distribution of size of molecular aggregates in chenodeoxycholic acid-rich bile was significantly different from that in ursodeoxycholic acid-rich bile. From the experiment of model bile solution, it was demonstrated that number and site of hydroxyl group and electric charge of side chain of bile acid were important factors to determine the size of molecular aggregates. The superiority or inferiority of these factors to the formation of large aggregates was the following order : bile acid with dihydroxyl group > with trihydroxyl group, bile acid with α-site of hydroxyl group > with β-site of hydroxyl group, and side chain with monoanionic form > with dianionic form.

L4 ANSWER 8 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
85027652 EMBASE Document No.: 1985027652. Serum concentrations of ursodeoxycholic acid in portal venous and systemic venous blood of fasting humans as determined by isotope dilution-mass spectrometry. Ewerth S.; Angelin B.; Einarsson K.; et al.. Department of Surgery, Karolinska Institutet at Huddinge University Hospital, S-141 86 Stockholm, Sweden. Gastroenterology 88/1 I (126-133) 1985.
CODEN: GASTAB. Pub. Country: United States. Language: English.

AB The fasting concentrations of ursodeoxycholic acid were determined in peripheral and portal venous serum of untreated (n = 12) and ursodeoxycholic acid-treated (n = 7) patients undergoing cholecystectomy.

The levels of ursodeoxycholic acid were also determined in peripheral venous serum of 9 healthy subjects before and during **treatment** with ursodeoxycholic acid. Ursodeoxycholic acid, as well as cholic, chenodeoxycholic, and deoxycholic acids, were analyzed by a highly specific method based on isotope dilution-mass spectrometry. The fasting peripheral venous serum concentration of total (unconjugated plus conjugated) ursodeoxycholic acid averaged 0.14 μmol/L in the untreated gallstone patients and 0.19 μmol/L in the healthy subjects. The corresponding value in portal venous serum was 0.44 μmol/L. **Treatment** with ursodeoxycholic acid raised the level of this bile acid about 25-fold in portal as well as in peripheral venous serum. The proportion of unconjugated ursodeoxycholic acid was 34% in portal and 49% in peripheral venous serum of treated subjects. The mean hepatic uptake of ursodeoxycholic acid was calculated to be about 60% both in untreated and treated subjects. This uptake was significantly lower than that of cholic acid (83%). The hepatic uptake of ursodeoxycholic acid also tended to be lower than that of chenodeoxycholic acid (68%). This was mainly due to a lower hepatic uptake of unconjugated ursodeoxycholic acid (34%) compared with unconjugated chenodeoxycholic acid (49%). The relatively low hepatic uptake of unconjugated ursodeoxycholic acid explains why serum levels of the administered bile acid are higher during **treatment** with ursodeoxycholic acid than during **treatment** with **chemodeoxycholic acid.** Our results also give evidence that the hepatic uptake of ursodeoxycholic acid cannot be saturated under physiologic conditions.

L4 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
1983:466925 Document No. 99:66925 Diagnosis of cerebrotendinous xanthomatosis (CTX) and effect of chenodeoxycholic acid therapy by analysis of urine using capillary gas chromatography. Wolthers, B. G.; Volmer, M.; Van der Molen, J.; Koopman, B. J.; De Jager, A. E. J.; Waterreus, R. J. (Cent. Lab. Clin. Chem., Univ. Hosp., Groningen, Neth.). Clinica Chimica Acta, 131(1-2), 53-65 (English) 1983. CODEN: CCATAR. ISSN: 0009-8981.

AB By means of capillary gas chromatog., urine samples of patients with CTX were investigated before and during **treatment** by oral administration of chenodeoxycholic acid. The occurrence of various conjugated bile alcs., presumably glucuronides, was demonstrated, the major compound being 5β-cholestane-3α,7α,12α,23ξ,2 5-pentol. In the bile acid fraction, norcholic acid and hydroxycholic acid were present in considerable amts. In this way, the presence of CTX can be demonstrated conclusively. After chenodeoxycholic acid therapy, the excretion of both abnormal bile acids as well as of bile alcs. rapidly decreased within a few weeks, showing the effectiveness of the **treatment.** By early discovery and subsequent therapy, it may be possible to prevent the onset of the detrimental symptoms, such as mental deficiency, caused by the accumulation of cholestanol and cholesterol in CTX patients.

L4 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1980:126317 Document No.: PREV198069001313; BA69:1313. HISTOLOGICAL AND HISTO ENZYMOLOGICAL STUDY OF THE LIVER 2. WITH CHENO DEOXY CHOLIC-ACID TREATED GALL STONES. LAGERON A [Reprint author]; LEVY V-G; SAFFROY M; VERTHIER N. INST NATL SANTE RECH MED, 184 RUE DU FAUBOURG SAINT-ANTOINE, F-75012 PARIS, FR. Acta Histochemica, (1979) Vol. 65, No. 1, pp. 8-14. CODEN: AHISA9. ISSN: 0065-1281. Language: FRENCH.

AB The histological and histochemical changes of liver from gallstones treated with **chemodeoxycholic acid** are confronted with the same livers before **treatment.** There was little modification in histological patterns but the frequency of sinusoidal congestion increased. Numerous histoenzymological injuries are corrected by this **treatment.**

L4 ANSWER 11 OF 13 MEDLINE on STN
78051542. PubMed ID: 927713. [Medical **treatment** of cholesterol

cholelithiasis using **chemodeoxycholic acid** in man].
Il trattamento medico della calcolosi biliare colesterolica nell'uomo con acido chenodesossicolico. Barbara L; Roda E; Roda A; Casanova S; Festi D; Sama C; Mazella G; Aldini R. Minerva medica, (1977 Oct 17) 68 (49) 3355-82. Journal code: 0400732. ISSN: 0026-4806. Pub. country: Italy. Language: Italian.

AB The results of a tiral using chenodeoxycholic acid in 400 patients with cholesterol gallstones are reported. The "qualifying points" of such **treatment** are compared with the literature data in clinical and laboratory terms. 54% of 300 in clinical and laboratory terms. 54% of 300 patients who received less than 12 mg/kg/day achieved dissolution in a mean time of 11 months, while 64% of the remainder (12-15 mg/kg/day) did so in an average of 8 months. Microcalculi proved most sensitive to **treatment** (65% of positive results). Lithiasis over 5 years standing and over-weight (10% over the ideal figure) were factors that imposed more protracted **treatment.** Careful selection of candidates was proved important by the results of quarterly liver and intestine performance examinations. These were more extensive and more clearly aimed than those proposed by other workers. They showed that the acid is neither hepato nor enterotoxic. Indeed, no serious side-effects were noted.

L4 ANSWER 12 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
78065214 EMBASE Document No.: 1978065214. [**Chemodeoxycholic acid** versus placebo in the **treatment** of gallstones].
ACIDE CHENIQUE CONTRE PLACEBO DANS LE TRAITEMENT DE LA LITHIASE BILIAIRE.
Concours Medical 99/15 (2345) 1977.
CODEN: COMEAO. Language: French.

L4 ANSWER 13 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
78036909 EMBASE Document No.: 1978036909. [**Treatment** of gallstones with **chemodeoxycholic acid**]. LE TRAITEMENT DE LA LITHIASE BILIARE PAR L'ACIDE CHENODEOXYCHOLIQUE. Petite J.P.. Serv. Med. Int. Hop. Broussais, Paris, France. Revue du Praticien 27/12 (757-759) 1977.
CODEN: REPRA3. Language: French.

=> s cholic acid
L5 22161 CHOLIC ACID

=> s l5 and chronic heart failure
L6 1 L5 AND CHRONIC HEART FAILURE

=> d l6 cbib abs

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
2000:645885 Document No. 133:217694 Endotoxin-modulating compounds for therapy of heart failure and cachexia. Anker, Stefan; Coats, Andrew; Volk, Hans-Dieter; Rauchhaus, Mathias; Schumann, Ralf Reiner (Max-Delbruck-Centrum fur Molekulare Medizin, Germany). PCT Int. Appl. WO 2000053224 A2 20000914, 74 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP2299 20000309. PRIORITY: GB 1999-5300 19990309; GB 1999-5307 19990309; GB 1999-5310 19990309; GB 1999-5314 19990309; GB 1999-5315 19990309.

AB A method of treating, preventing or ameliorating chronic or acute heart

failure in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, bile acids, or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. A method of treating, preventing or ameliorating endotoxin-mediated immune activation in acute or **chronic heart failure** in a
patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, bile acids or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. Also disclosed is a method for treating cachexia and wasting syndromes due to diseases other than congestive heart failure.

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=> s deoxycholic acid
L7        13576 DEOXYCHOLIC ACID

=> s l7 and treatment
L8         1991 L7 AND TREATMENT

=> s l8 adn chronic heart failure
MISSING OPERATOR L8 ADN
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l8 and chronic heart failure
L9            0 L8 AND CHRONIC HEART FAILURE

=> s LPS
L10      138882 LPS

=> s l10 and heart failure
L11         266 L10 AND HEART FAILURE

=> s l11 and treatment
L12          89 L11 AND TREATMENT

=> dup remove l12
PROCESSING COMPLETED FOR L12
L13          46 DUP REMOVE L12 (43 DUPLICATES REMOVED)

=> d l13 1-46 cbib abs

L13  ANSWER 1 OF 46     MEDLINE on STN                    DUPLICATE 1
2004237705.    PubMed ID: 15135663.   Cytokines are not upregulated in
     adriamycin-induced cardiomyopathy and heart failure.
     Lou H; Danelisen I; Singal P K. (Institute of Cardiovascular Sciences, St.
     Boniface General Hospital Research Centre, Faculty of Medicine, University
     of Manitoba, Room 3022, 351 Tache Avenue, Winnipeg, Man., Canada R2H 2A6.
     ) Journal of molecular and cellular cardiology, (2004 May) 36 (5) 683-90.
     Journal code: 0262322. ISSN: 0022-2828. Pub. country: England: United
     Kingdom. Language: English.
AB   Heart failure due to a variety of causes is
```

accompanied by an upregulation of cytokines, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta) and interleukin-6 (IL-6). Adriamycin-induced cardiomyopathy (AIC) and **heart failure** is an important clinical problem. The current study investigated the expression of these cytokines in AIC and **heart failure** in rats. Both early and late stages of AIC was produced in rats. Myocardial gene expressions for TNF-alpha, IL-1beta and IL-6 were examined with DNA microarrays and RT-PCR. Protein levels of these cytokines in both the plasma and the myocardium were also examined by ELISA. In the early stage, myocardial mRNA expression of IL-1beta showed significant increase at 4 and 24 h, peaking at 4 h, while TNF-alpha did not change and IL-6 was undetectable. The protein levels of these three genes did not show any upregulation in the plasma or the heart. In the late stage, **heart failure** was confirmed by clinical signs as well as homodynamic changes. In this stage, plasma protein levels for TNF-alpha, IL-1beta and IL-6 were not changed. However, myocardial TNF-alpha mRNA expression and protein levels were significantly decreased, while both IL-1beta mRNA and protein levels were not different compared to the control group. IL-6 mRNA expression was undetectable in both normal and adriamycin-treated hearts while its protein level was not changed by adriamycin. Positive control using lipopolysaccharides (**LPS**) **treatment** (0.5 mg/kg body weight) for 2 h resulted in a significant increase in these three cytokines in the heart and plasma. These data suggest that an upregulation of cytokines may not be involved in AIC. **Heart failure** may in fact be accentuated by a downregulation of myocardial TNF-alpha.

L13 ANSWER 2 OF 46 MEDLINE on STN DUPLICATE 2

2004283437. PubMed ID: 15182775. Selective intestinal decontamination in advanced chronic **heart failure**: a pilot trial.

Conraads Viviane M; Jorens Philippe G; De Clerck Luc S; Van Saene Hendrik K; Ieven Margaretha M; Bosmans Johan M; Schuerwegh Annemie; Bridts Chris H; Wuyts Floris; Stevens Wim J; Anker Stefan D; Rauchhaus Mathias; Vrints Christiaan J. (Department of Cardiology, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium.) European journal of heart failure : journal of the Working Group on Heart Failure of the European Society of Cardiology, (2004 Jun) 6 (4) 483-91. Journal code: 100887595. ISSN: 1388-9842. Pub. country: Netherlands. Language: English.

AB Background and aims: Endotoxin, derived from intestinal aerobic Gram-negative bacilli (AGNB), could be an important monocyte activator in chronic **heart failure** (CHF). The effect of selective decontamination of the digestive tract (SDD) on intracellular monocyte cytokine production, monocyte CD14 expression, circulating endotoxin and cytokines, and flow-mediated dilation (FMD) was studied in patients with severe CHF. Methods and results: Ten patients with CHF (NYHA class III-IV) were enrolled in a non-placebo controlled pilot trial involving the administration of SDD (polymyxin B, tobramycin) for 8 weeks. One patient was later excluded due to cardiac transplantation. Before **treatment**, after 4 and 8 weeks therapy, and 6 weeks post-**treatment**, monocyte CD14 expression, intracellular monocyte production of interleukin-1beta [IL-1beta], interleukin-6 [IL-6], tumour necrosis factor (TNF)-alpha with and without lipopolysaccharide (**LPS**) stimulation were measured. Concentrations of endotoxin and cytokines (IL-1beta, IL-6, TNF-alpha) were also determined. AGNB in faeces, intestinal endotoxin and FMD were assessed at baseline, after 4 weeks of **treatment** and 6 weeks post-**treatment.** SDD eradicated intestinal AGNB ($P<0.00001$) and decreased faecal endotoxin concentrations ($P<0.00001$). There was a significant decline in monocyte CD14 expression ($P=0.03$) and in IL-1beta ($P=0.0001$), IL-6 ($P=0.02$) and TNF-alpha ($P=0.0002$) production after 4 and 8 weeks of **treatment** in the basal state and for IL-1beta ($P=0.008$) and IL-6 ($P=0.005$) after **LPS** stimulation. FMD significantly improved at 4 weeks and returned to baseline after **treatment** discontinuation ($P=0.002$). Circulating concentrations of endotoxin and cytokines remained unchanged. Conclusion: Reduction of the intestinal endotoxin pool led to a decrease

in monocyte CD14 expression and intracellular cytokine production in patients with severe CHF. The improvement of peripheral endothelial function could be a marker of the anti-inflammatory effect of SDD.

L13 ANSWER 3 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2004051205 EMBASE Altered expression of nuclear hormone receptors and coactivators in mouse heart during the acute-phase response. Feingold K.; Kim M.S.; Shigenaga J.; Moser A.; Grunfeld C.. K. Feingold, Metabolism Section (111F), Dept. of Vet. Affairs Medical Center, 4150 Clement St., San Francisco, CA 94121, United States. kfngld@itsa.ucsf.edu. American Journal of Physiology - Endocrinology and Metabolism 286/2 49-2 (E201-E207) 2004.
Refs: 66.
ISSN: 0193-1849. CODEN: AJPMD. Pub. Country: United States. Language: English. Summary Language: English.

AB Severe sepsis results in the decreased uptake and oxidation of fatty acids in the heart and cardiac failure. Some of the key proteins required for fatty acid uptake and oxidation in the heart have been shown to be downregulated after endotoxin (**LPS**) administration. The nuclear hormone receptors, peroxisome proliferator-activated receptor (PPAR) and thyroid receptor (TR), which heterodimerize with the retinoid X receptor (RXR), are important regulators of fatty acid metabolism and decrease in the liver after **LPS** administration. In the present study, we demonstrate that **LPS treatment** produces a rapid and marked decrease in the mRNA levels of all three RXR isoforms, PPARα and PPARδ, and TRα and TRβ in the heart. Moreover, **LPS** administration also decreased the expression of the coactivators CREB-binding protein (CBP)/p300, steroid receptor coactivator (SRC)-1, SRC-3, TR-associated protein (TRAP)220, and PPARγ coactivator (PGC)-1, all of which are required for the transcriptional activity of RXR-PPAR and RXR-TR. In addition, the mRNA levels of the target genes malic enzyme, Spot 14, sarcoplasmic reticulum Ca(2+)-ATPase, or SERCA2, the VLDL receptor, fatty acyl-CoA synthetase, fatty acid transporter/CD36, carnitine palmitoyltransferase Iβ, and lipoprotein lipase decrease in the heart after **LPS treatment.** The decrease in expression of RXRα, -β, and -γ, PPARα and -δ, and TRα and -β, and of the coactivators CBP/p300, SRC-1, SRC-3, TRAP220, and PGC-1 and the genes they regulate, induced by **LPS** in the heart, could account for the decreased expression of key proteins required for fatty acid oxidation and thereby play an important role in cardiac contractility. These alterations could contribute to the myocardial dysfunction that occurs during sepsis.

L13 ANSWER 4 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2003:509992 The Genuine Article (R) Number: 688AZ. Atrial natriuretic peptide polarizes human dendritic cells toward a Th2-promoting phenotype through its receptor guanylyl cyclase-coupled receptor A. Morita R; Ukyo N; Furuya M; Uchiyama T; Hori T (Reprint). Kyoto Univ, Grad Sch Med, Dept Hematol & Oncol, Sakyo Ku, 54 Shogoin Kawara Cyo, Kyoto 6068507, Japan (Reprint); Kyoto Univ, Grad Sch Med, Dept Hematol & Oncol, Sakyo Ku, Kyoto 6068507, Japan; Suntory Inst Biomed Res, Osaka, Japan. JOURNAL OF IMMUNOLOGY (15 JUN 2003) Vol. 170, No. 12, pp. 5869-5875. Publisher: AMER ASSOC IMMUNOLOGISTS. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. ISSN: 0022-1767. Pub. country: Japan. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Atrial natriuretic peptide (ANP) is a cardiovascular hormone secreted mainly by the cardiac atria and regulates the volume-pressure homeostasis. The action of ANP is mediated by its receptor, guanylyl cyclase-coupled receptor A (GC-A). In this study, we explored the possibility that ANP and GC-A may play a role in the dendritic cell (DC)-mediated immune regulation. We first examined the expression of GGA in human monocyte-derived DCs in comparison with monocytes and found that DCs but not monocytes express GC-A at both the mRNA and protein levels. DCs responded to ANP with an increase in intracellular cGMP in a

dose-dependent manner, indicating that GC-A expressed on DCs is functional. Furthermore, **treatment** of DCs with ANP decreased production of IL-12 and TNF-alpha and conversely increased that of IL-10 upon stimulation with **LPS**. In accordance with this change of cytokine production, DCs treated with ANP plus **LPS** promoted differentiation of naive CD4(+) T cells into a Th2 phenotype. Finally, we presented evidence that ANP affected cytokine production of fresh whole blood stimulated with **LPS** in line with the above-mentioned results. These results indicate that ANP polarizes human DCs toward a Th2-promoting phenotype through GC-A and thus can regulate immune responses.

L13 ANSWER 5 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003403291 EMBASE Urgent thoracic aortal dissection and aneurysm: **Treatment** with stent-graft implantation in an angiographic suite.

Balzer J.O.; Doss M.; Thalhammer A.; Fieguth H.-G.; Moritz A.; Vogl T.J.. J.O. Balzer, Dept. of Diagn./Intervent. Radiology, University Clinic Frankfurt/Main, Johann Wolfgang Goethe University, Theodor-Stern-Kai 7, 60590 Frankfurt, Main, Germany. j.o.balzer@em.uni-frankfurt.de. European Radiology 13/10 (2249-2258) 1 Oct 2003.

Refs: 22.

ISSN: 0938-7994. CODEN: EURAE3. Pub. Country: Germany. Language: English. Summary Language: English.

AB The aim of this study was to evaluate the feasibility of endoluminal stent-graft placement in an angiographic suite for the **treatment** of emergent type-B aortic dissections and ruptured thoracic aortal aneurysms. Twenty-six patients with either urgent type-B dissection (n=8) or aneurysms (n=18) of the descending thoracic aorta were chosen for stent-graft implantation. All patients received a multidetector-row CT angiography of the whole aorta and pelvic arteries prior to stent-graft implantation. All procedures were performed in a fully equipped digital subtraction angiography (DSA) suite under general anesthesia. In 20 patients Talent **LPS** tube grafts and in 4 patients an Excluder graft were used. Access was achieved via surgical cut-down in the left (n=7) or right (n=19) groin. Sealing was successful in 24 patients. The proximal covered portion of the stent graft was placed across the left subclavian artery in 2 patients. Procedural success was achieved in 23 of 24 patients. One patient required a second stent-graft placement before the aneurysm was sealed. One patient with an acute perforation of the descending aorta died due to cardiac failure prior to stent-graft implantation. In 1 patient stent-graft delivery failed due to severe calcification of both common iliac arteries. Endoluminal **treatment** of both urgent type-B aortic dissections and thoracic aortal aneurysms with stent graft is an attractive alternative **treatment** to surgical repair. The placement of stent grafts in an angiographic suite is a safe and feasible method with good clinical effectiveness and, so far, good clinical outcome.

L13 ANSWER 6 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003363662 EMBASE Acceptable short-term results after endovascular repair of diseases of the thoracic aorta in high risk patients. Krohg-Sorensen K.; Hafsahl G.; Fosse E.; Geiran O.R.. K. Krohg-Sorensen, Dept. of Thorac./Cardiovasc. Surgery, Rikshositalet University Hospital, N-0027 Oslo, Norway. kirsten.krohg-sorensen@rikshospitalet.no. European Journal of Cardio-thoracic Surgery 24/3 (379-387) 1 Sep 2003.

Refs: 15.

ISSN: 1010-7940. CODEN: EJCSE7. Pub. Country: Netherlands. Language: English. Summary Language: English.

AB Objective: To report our experience with endovascular stentgraft repair of diseases of the descending thoracic aorta in high risk patients. Methods: Twenty-one procedures were performed in 20 patients (10 women), aged 22-81 years, for disease of the descending thoracic aorta with the Gore Excluder thoracic endoprosthesis® (WL Gore) (n=11) and the Talent **LPS**

Stent Graft System (Medtronic AVE) (n=10). All patients were considered high operative risk. Diagnoses included saccular aneurysm, aneurysm rupture, mycotic aneurysm, penetrating atherosclerotic ulcer, aortic dissection and aortitis. The access vessels were a tube graft of the (thoraco-) abdominal aorta (n=4), the common iliac (n=6) and the common femoral artery (n=11). Several patients needed major cardiovascular surgery for concomitant disease during the same stay. Computed tomography scan and chest X-ray was performed at 3 and 6 months and thereafter every sixth month postoperatively. Results: Two patients died. One had a colon perforation 8 days postoperatively and died after 3.5 months, and the other with preoperative sepsis and a mycotic aneurysm died on day 11 from cardiac and renal failure. In one patient the stentgraft dislocated during release, and an additional stentgraft had to be implanted 1 week later to treat the proximal leak. In another patient the stentgraft could not be released from the introducer, and was pulled back to the aortic bifurcation and retrieved through laparotomy. Eighteen patients have been followed for 1-24 months, and no migration, wire fractures or endoleak have been seen. There were no neurologic complications. One patient treated for infected pseudoaneurysm had a chronic graft infection. Conclusion: In this small number of patients with high operative risk, short-term results of endovascular stentgraft repair of variable diseases of the descending aorta have been satisfactory. Stentgraft repair could be a valuable supplement to surgery for patients with complex multilevel or multiorgan disease.

L13 ANSWER 7 OF 46 EMBASE
on STN DUPLICATE 3

2003497219 EMBASE Interleukin-1β mediates endotoxin- and tumor necrosis factor α-induced RGS16 protein expression in cultured cardiac myocytes. Patten M.; Stube S.; Thoma B.; Wieland T.. M. Patten, Zentrum fur Innere Medizin, III, Medizinische Klinik, Univ. Klin. Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. patten@uke.uni-hamburg.de. Naunyn-Schmiedeberg's Archives of Pharmacology 368/5 (360-365) 2003.
Refs: 34.
ISSN: 0028-1298. CODEN: NSAPCC. Pub. Country: Germany. Language: English. Summary Language: English.

AB Endotoxin (**LPS**)-induced cardiac failure is associated with an up-regulation of RGS16 protein expression and repression of phospholipase C activity in vivo. Since the release of pro-inflammatory cytokines plays an important role in mediating **LPS**-induced myocardial dysfunction, we examined the effect of recombinant cytokines on the expression of RGS16 protein in neonatal cardiac myocytes. Myocytes in culture were treated with 50 ng/ml recombinant tumor necrosis factor α (TNFα), 2 ng/ml interleukin 1β (IL-1β), interleukin 6 (IL-6), interferon γ (IFNγ) or diluent (NaCl) for 24 h. Before stimulation with **LPS** (4 μg/ml for 24 h) cells were treated with 200 ng/ml interleukin 1-receptor antagonist (IL-1ra), 500 ng/ml soluble TNF receptor (sTNFr), or NaCl for 1 h. Isolated membrane proteins were used for Western blot analysis. Cell-associated and secreted IL-1β and TNFα protein content were determined in myocyte protein homogenates and cell culture supernatants by ELISA immunoblotting 3, 6, 24, 48 and 72 h after **treatment** with **LPS**. IL-1β (1.75-fold) and TNFα (1.62-fold) but not IL-6 and IFNγ induced RGS16 protein expression. **LPS** stimulated intracellular IL-1β expression within 6 h (847.1±172.9 pg/ 3x10(6) cells) followed by an increase in extracellular secretion up to 70.8±8.1 pg/3x10(6) cells after 48 h. In contrast, intracellular protein concentrations of TNFα were almost not detectable (0.03±0.01 pg/3x10(6) cells), but extracellular secretion was induced by **LPS** with a maximum at 6 h (653.9±36.3 pg/3x10(6) cells). The **LPS**-induced increase in RGS16 (1.6-fold) was blunted by IL-1ra but not by TNFα scavenging. Interestingly, both, the IL-1β- and TNFα-effect could be blocked by IL-1ra, indicating that also the TNFα-induced RGS16

expression is mediated by IL-1. We therefore conclude that **LPS** induces RGS16 protein expression by activation of the cytokine IL-1β in cardiac myocytes. Our data substantiate the role of IL-1β as an important mediator in **LPS**-induced cardiac failure.

L13 ANSWER 8 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:576101 The Genuine Article (R) Number: 697RP. Myocardial IL-6 regulation by neurohormones - an in vitro superfusion study. Jeron A (Reprint); Kaiser T; Straub R H; Weil J; Riegger G A J; Muders F. Klinikum Univ Regensburg, Klin & Poliklin Innere Med 2, Franz Josef Strauss Allee 11, D-93042 Regensburg, Germany (Reprint); Klinikum Univ Regensburg, Klin & Poliklin Innere Med 2, D-93042 Regensburg, Germany; Klinikum Univ Regensburg, Klin & Poliklin Innere Med 1, D-93042 Regensburg, Germany. BRAIN BEHAVIOR AND IMMUNITY (AUG 2003) Vol. 17, No. 4, pp. 245-250. Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA. ISSN: 0889-1591. Pub. country: Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Interleukin-6 (IL-6) is expressed in the myocardium and has been implicated in cell proliferation, negative inotropic effects and myocardial hypertrophy. To determine whether myocardial IL-6 is modified by neuro-humoral and immunoregulatory stimuli, we studied the effects of lipopolysaccharide (**LPS**), corticosterone (CS), isoproterenol and angiotensin II on myocardial IL-6 secretion in superfused myocardium.

Methods: Slices of rat left ventricular myocardium were superfused in 80 mul chambers for up to 5 h. **LPS** (1, 50, and 100 mug/ml), CS (10(-7), 10(-6), and 10(-5) M, DSMO as vehicle), isoproterenol (10(-6), 10(-7), and 10(-8) M) and angiotensin II (10(-5), 10(-7), and 10(-9) M) were added to the culture medium at hour 2. IL-6 was measured in the perfusate by ELISA.

Results: Physiological corticosterone concentrations (10(-7) M) resulted in an increase in IL-6 concentration (142%) while high doses of steroid decreased IL-6 significantly (CS 10(-6) M: 88 +/- 14%, p <.05; CS 10(-5): 91 +/- 9%, p < .05) after 5 h. Left ventricular IL-6 secretion was significantly stimulated by **LPS** 50 mug/ml (3262 1684% vs. CTRL: 116 +/- 134%, p < .01). Isoproterenol **treatment** increased in IL-6 secretion compared to controls with and without CS, while angiotensin II reduced IL-6 concentration only in combination with CS.

Conclusion: Myocardial IL-6 secretion is modulated by physiological concentrations of corticosterone or angiotensin II and can be induced by **LPS** or isoproterenol, indicating a tight regulation of this cytokine. Suppression of cytokine expression within the heart might be a potential therapeutic goal in the **treatment** of various cardiovascular diseases. (C) 2003 Elsevier Science (USA). All rights reserved.

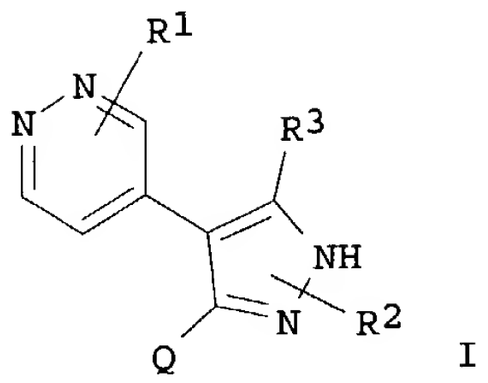
L13 ANSWER 9 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:932472 The Genuine Article (R) Number: 736CF. Effects of enalapril on disseminated intravascular thrombin formation during systemic inflammation . Marsik C; Graninger M; Mackman N; Osterud B; Luther T; Jilma B (Reprint). Univ Vienna, Dept Clin Pharmacol, Div Haematol & Immunol, Waehringer Guertel 18-20, A-1090 Vienna, Austria (Reprint); Univ Vienna, Dept Clin Pharmacol, Div Haematol & Immunol, A-1090 Vienna, Austria; Univ Vienna, Inst Med & Chem Lab Diagnost, Vienna, Austria; Scripps Res Inst, Dept Immunol & Vasc Biol, La Jolla, CA USA; Univ Tromso, Inst Biochem, Tromso, Norway; Univ Dresden, Inst Pathol, Dresden, Germany. CARDIOVASCULAR RESEARCH (15 OCT 2003) Vol. 60, No. 1, pp. 131-135. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0008-6363. Pub. country: Austria; USA; Norway; Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Tissue factor (TF), the main trigger of coagulation is important in the propagation of cardiovascular diseases. Based on an in vitro study, we hypothesised that enalapril may blunt the endotoxin-induced, TF-triggered coagulation in humans. Methods: In a randomised, controlled trial, 30 healthy male volunteers received 2 ng/kg

of lipopolysaccharide (**LPS**) after pre-**treatment** with placebo or enalapril for 5 days or with enalapril 2 h before **LPS** infusion. Results: Infusion of **LPS** increased interleukin-6 levels 400 fold, and induced a 10-fold increase in prothrombin fragment, a fourfold increase in D-dimer, and a fivefold increase in plasmin-antiplasmin complexes. However, pre-**treatment** with enalapril did not blunt **LPS**-induced coagulation. Conclusions: Our trial provides evidence against a modulatory role of angiotensin converting enzyme in **LPS**-induced, TF-triggered coagulation. (C) 2003 European Society of Cardiology. Published by Elsevier B.V. All rights reserved.

L13 ANSWER 10 OF 46 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2003:258367 Document No.: PREV200300258367. Cytokine upregulation in **heart failure** may not be a universal phenomenon. Lou, Huiquan [Reprint Author]; Danelisen, Igor; Singal, Pawan K.. Physiology, Institute of Cardiovascular Sciences, 351 Tache Avenue, Winnipeg, Manitoba, R2H 2A6, Canada. louhuiq@hotmail.com; umdaneli@cc.umanitoba.ca; pawan_singal@sbrc.ca. FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 344.2. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. San Diego, CA, USA. April 11-15, 2003. FASEB.
ISSN: 0892-6638 (ISSN print). Language: English.
AB Background: **Heart failure** due to a variety of causes is generally accompanied by up-regulation of cytokines, such as TNF-(, IL-1(and IL-6. The current study investigated the expression of these cytokines in Adriamycin-induced cardiomyopathy and **heart failure** in rats. Methods: Both early and late-stage adriamycin-induced cardiomyopathy was produced in rats. Myocardial gene expression for cytokines, TNF-(, IL-1(and IL-6 was examined with DNA microarrays and RT-PCR. The protein levels of these cytokines in both plasma and myocardium were also studied by ELISA. Results and Conclusion: In the early stage, none of the three genes showed any up-regulation in both plasma and heart. During the late-stage **heart failure** was confirmed by clinical signs as well as homodynamic changes. In this stage, plasma TNF-(, IL-1(and IL-6 protein levels were not changed. However, myocardial TNF-(mRNA expression and protein levels were decreased, while both IL-1(mRNA and protein levels were not different compared to the control group. IL-6 mRNA expression was undetectable in both normal and ADR treated hearts. Positive control using lipopolysaccharides (**LPS**) **treatment** resulted in a significant increase in these three cytokines in the heart and plasma. DNA microarray analysis did not show gene expression both in control and adriamycin groups. These data suggest that TNF-(, IL-1(and IL-6 may not be involved in adriamycin-induced cardiomyopathy and **heart failure.**

L13 ANSWER 11 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
2002:888734 Document No. 137:384849 Preparation of 4-(4-pyridazinyl)pyrazole derivatives as p38MAP kinase (p38 mitogen-activated protein kinase) inhibitors. Minami, Nobuyoshi; Hasumi, Koichi; Ohta, Shuji; Sato, Shuichiro; Saito, Takahisa; Doi, Satoshi; Kobayashi, Motohiro; Sato, Jun; Asano, Hajime; Matsumoto, Yasuhiro (Teikoku Hormone Mfg. Co., Ltd., Japan). PCT Int. Appl. WO 2002092593 A1 20021121, 66 pp. DESIGNATED STATES: W: AU, CA, CN, JP, KR, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (Japanese). CODEN: PIXXD2.
APPLICATION: WO 2002-JP4636 20020514. PRIORITY: JP 2001-146270 20010516.
GI



I

AB 4-(4-Pyridazinyl)pyrazole derivs. represented by the following general formula (I) or salts thereof [wherein Q = optionally substituted aryl or heteroaryl; R1 = H, halogeno, HO, lower alkoxy, NH2, aralkylamino, mono- or di(lower alkyl)amino, lower alkylthio; R2 = H, lower alkynyl, optionally hydroxy-substituted lower alkyl; R3 = H, lower alkyl, CH2CH(R4)-(A)n-Y, CH:C(R4)-(A)n-Y, CH2CH(R4)-(A)n-Y, NR4-CO-(A)n-Y, lower cycloalkyl (wherein A = lower alkylene; Y = (un)substituted aryl; R4 = H, lower alkyl; n = 0, 1)] are prepared These compds. have an excellent inhibitory activity on p38 mitogen-activated protein kinase (p38MAPK), which is known to activate certain transcription factors such as TNF-κB, AP-1, and CREB binding to a DNA sequence common to tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and cyclooxygenase II (COX-II) and thus promoting the transcription and production of proteins such as TNF-α, IL-1, IL-6, and COX-II from mRNA. Thereby they inhibit the production of TNF-α, IL-1, IL-6, and COX-II and are useful for preventing or treating diseases associated with TNF-α, IL-1, IL-6, and COX-II. The above diseases include chronic articular rheumatism, multiple sclerosis, osteoarthritis (arthrosis deformans), psoriasis, HIV, asthma, septic shock, inflammatory bowel diseases, Crohn's disease, Alzheimer's disease, diabetes, cachexia, osteoporosis, graft-vs.-host disease, adult respiratory distress syndrome, arteriosclerosis, gout, glomerulonephritis, congestive **heart failure**, ulcerative colitis, septicemia, cerebral malaria, restenosis, hepatitis, systemic lupus erythematosus, thrombosis, born resorption disease, chronic pulmonary inflammation disease, heart reperfusion disorder, kidney reperfusion disorder, cancer, writer's syndrome, imminent abortion, eczema, allograft rejection, or seizure. They also include fever, Behcet's disease, neuralgia, meningitis, sunburn, contact dermatitis, acute synovitis, spondylitis, muscle degeneration, neovascularization, conjunctivitis, psoriatic arthritis, viral myocarditis, pancreatitis, hemorrhage, arthritis, endotoxin shock, parasitic infection, tuberculosis, myocardial infarction, Hansen's disease, diabetic retinopathy, irritable bowel syndrome (IBS), transplant rejection, burn, bronchitis, ischemic heart disease, eclampsia, pneumonia, remission of swelling, backache (low back pain), pharyngolaryngitis (pharyngitis-laryngitis), Kawasaki disease (mucocutaneous lymphnode syndrome), spinal cord disease, or atopic dermatitis. Thus, 2.0 M LiN(CHMe2)2/heptane-THF-ethylbenzene was added dropwise to a solution of 3.83 g 4-methylpyridazine in 40 mL THF at -70° and stirred at room temperature, followed by adding a solution of 6.84 g Et 4-fluorobenzoate in 40 mL THF at -70°, and the resulting mixture was stirred at room temperature for 3 h to give 40% 1-fluoro-4-(4-pyridazinylacetyl)benzene (II). To a solution of 4 g II in 80 mL THF was added 4.41 g N,N-dimethylformamide di-Me acetal and stirred at room temperature for 20 h, followed by distilling off the solvent under reduced pressure, and the residue was dissolved in 60 mL ethanol, treated with 1.85 g hydrazine monohydrate, and stirred at 50° for 30 min to give 79% 3(5)-(4-fluorophenyl)-4-(4-pyridazinyl)pyrazole (III). In a p38MAP kinase-binding inhibitory assay, III in vitro showed IC50 of 6.5 nM for inhibiting the binding of a radioligand, [3H]-SB202190, i.e. 4-(4-fluorophenyl)-2-(4-hydroxy-3,4-di-3H-phenyl)-5-(4-pyridyl)imidazole,

on cytosol of human monocyte THP-1 cell. III at 30 mg/kg in vivo inhibited the lipopolysaccharide (**LPS**)-induced production of TNF-α in mice by 84% after 6 h.

L13 ANSWER 12 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
2002:315096 Document No. 136:320419 Human IL-17-related protein LP-48 and therapeutic use thereof. Glasebrook, Andrew Lawrence; Liu, Ling; Newton, Christy Michelle; Tetreault, Jonathan Wendell (Eli Lilly and Company, USA). PCT Int. Appl. WO 2002033083 A2 20020425, 112 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US27737 20010928. PRIORITY: US 2000-PV240177 20001013; US 2001-PV309936 20010803.

AB The invention provides protein and cDNA sequences for a novel human IL-17-related protein called LP-48 (also known as IL-17C and IL-21), which is a member of interleukin superfamily. The transgenic mice expressing LP-48 are used to test the function of LP-48 and possible therapeutic applications. LP-48 can protect the transgenic mice against **LPS**-induced septic shock and from **LPS**-induced death. LP-48 protein can inhibit **LPS**-induced increases in IFN-γ, IL-12, TNF-α and IL-6 secretion in transgenic mice. LP-48 can reduce apoptosis in human endothelial cells, more specifically, apoptosis induced by staurosporine. LP-48 can bind to the cell surface of endothelial cells and other tissues specifically through natural LP-48 receptors. Methods are provided for the **treatment** or prevention of atherosclerosis, allergic autoimmune diseases, endothelial cell apoptosis, allograft vasculopathy, hypertension, congestive **heart failure**, ischemia/reperfusion injury, type 1 diabetes, inflammation, immunodeficiencies, cancers, and infectious diseases by administering a human IL-17 related polypeptide and/or an antibody recognizing an epitope thereof to a patient in need of such therapy.

L13 ANSWER 13 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
2002:872620 Document No. 138:252737 Role of poly(ADP-ribose) polymerase activation in endotoxin-induced cardiac collapse in rodents. Pacher, Pal; Cziraki, Attila; Mabley, Jon G.; Liaudet, Lucas; Papp, Lajos; Szabo, Csaba (Inotek Corporation, Beverly, MA, 01915, USA). Biochemical Pharmacology, 64(12), 1785-1791 (English) 2002. CODEN: BCPCA6. ISSN: 0006-2952. Publisher: Elsevier Science Inc..

AB Reactive oxygen and nitrogen species are overproduced in the cardiovascular system during circulatory shock. Oxidant-induced cell injury involves the activation of poly(ADP-ribose) polymerase (PARP). Using a dual approach of PARP-1 suppression, by genetic deletion or pharmacol. inhibition with the new potent phenanthridinone PARP inhibitor PJ34 [the hydrochloride salt of N-(oxo-5,6-dihydro-phenanthridine-2-yl)-N,N-dimethylacetamide], we studied whether the impaired cardiac function in endotoxic shock is dependent upon the PARP pathway. Escherichia coli endotoxin (lipopolysaccharide, **LPS**) at 55 mg/kg, i.p., induced a severe depression of the systolic and diastolic contractile function, tachycardia, and a reduction in mean arterial blood pressure in both rats and mice. **Treatment** with PJ34 significantly improved cardiac function and increased the survival of rodents. In addition, **LPS**-induced depression of left ventricular performance was significantly less pronounced in PARP-1 knockout mice (PARP-/-) as compared with their wild-type littermates (PARP+/+). Thus, PARP activation in the cardiovascular system is an important contributory factor to the cardiac collapse and death associated with endotoxin shock.

L13 ANSWER 14 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN DUPLICATE 4

2002339688 EMBASE Lethal effect of cytokine-induced nitric oxide and peroxynitrite on cultured rat cardiac myocytes. Keira N.; Tatsumi T.; Matoba S.; Shiraishi J.; Yamanaka S.; Akashi K.; Kobara M.; Asayama J.; Fushiki S.; Fliss H.; Nakagawa M.. Dr. T. Tatsumi, Second Department of Medicine, Kyoto Prefect. Univ. of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan. tatsumi@koto.kpu-m.ac.jp. Journal of Molecular and Cellular Cardiology 34/5 (583-596) 2002.
Refs: 52.
ISSN: 0022-2828. CODEN: JMCDAY. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB We examined the cytotoxic effect of iNOS-generated NO in cultured cardiac myocytes treated with IL-1β, IFN-γ and **LPS.** **Treatment** of the myocytes with cytokines for 48 h resulted in a marked NO production, a significant decline in cellular ATP content, and a significant increase in myocyte death with morphological characteristics of necrosis. Moreover, immunohistochemical examination showed that the cytokines caused nitrotyrosine formation in the injured myocytes. Uric acid and L-cysteine which have the ability to quench peroxynitrite significantly attenuated these cytokine-induced effects. although they did not alter NO production or the decline in cellular ATP. These data suggest that NO production induced by cytokines can not only cause deleterious effects in the myocardial energy balance but also induce myocytes necrosis, through the formation of peroxynitrite.

L13 ANSWER 15 OF 46 EMBASE
on STN

2002294975 EMBASE Effect of interleukin-10 on the production of tumor necrosis factor-alpha by peripheral blood mononuclear cells from patients with chronic **heart failure.** Bolger A.P.; Sharma R.; Von Haehling S.; Doehner W.; Oliver B.; Rauchhaus M.; Coats A.J.S.; Adcock I.M.; Anker S.D.. A.P. Bolger, Department of Clinical Cardiology, National Heart and Lung Institute, London SW3 6LY, United Kingdom. a.bolger@ic.ac.uk. American Journal of Cardiology 90/4 (384-389) 15 Aug 2002.
Refs: 29.
ISSN: 0002-9149. CODEN: AJCDAG.
Publisher Ident.: S 0002-9149(02)02494-3. Pub. Country: United States. Language: English. Summary Language: English.

AB Chronic **heart failure** (HF) is a state of inflammatory immune activation characterized by elevated circulating levels of tumor necrosis factor-α (TNF-α). Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine that inhibits TNF-α production and lessens endotoxin bioactivity. It is not known whether IL-10 reduces lipopolysaccharide (**LPS**) stimulated TNF-α production of peripheral blood mononuclear cells (PBMCs) from patients with chronic HF. PBMCs were isolated from 15 patients with chronic HF (New York Heart Association functional class 3.0 ± 0.2, left ventricular ejection fraction 30 ± 2%, peak oxygen consumption 18.1 ± 0.8 ml/kg/min) and 15 healthy control subjects and stimulated with 1 and 10 ng/ml **LPS** for 24 hours with or without prior addition of IL-10 (10 ng/ml). TNF-α was quantified in cell-free supernatants by an enzyme-linked immunosorbent assay. TNF-α, soluble TNF receptors, IL-10, and **LPS** were quantified in plasma. **LPS** stimulated TNF-α production was highest in those patients in New York Heart Association class II ($p < 0.01$ vs New York Heart Association class III and IV, $p < 0.001$ vs control subjects). IL-10 reduced PBMC TNF-α production in all stimulated samples at 1 and 10 ng/ml **LPS** (mean reduction 43% at 1 ng/ml, $p < 0.01$ and 55% at 10 ng/ml, $p < 0.0001$). The percentage reduction in TNF-α release did not differ significantly between patients and control subjects or with respect to severity of chronic HF or baseline immune parameters. Independently of clinical severity, IL-10 profoundly inhibits TNF-α release from PBMCs isolated from patients with chronic HF. IL-10 is, therefore, a potential

therapy for use in chronic HF associated with inflammatory immune activation. .COPYRGT. 2002 by Excerpta Medica, Inc.

L13 ANSWER 16 OF 46 MEDLINE on STN
2002652985. PubMed ID: 12411981. Preclinical and clinical assessment of the safety and potential efficacy of thalidomide in **heart failure.** Agoston Ildiko; Dibbs Ziad I; Wang Feng; Muller George; Zeldis Jerome B; Mann Douglas L; Bozkurt Biykem. (Winters Center for Heart Failure Research, Cardiology Section, Department of Medicine, Veterans Affairs Medical Center, Baylor College of Medicine, Houston, Texas 77030, USA.) Journal of cardiac failure, (2002 Oct) 8 (5) 306-14. Journal code: 9442138. ISSN: 1071-9164. Pub. country: United States. Language: English.

AB BACKGROUND: Inflammatory mediators, especially tumor necrosis factor (TNF), have been implicated in **heart failure** (HF). Thalidomide has anti-inflammatory properties and selectively inhibits TNF. Thus far, thalidomide or thalidomide analogues have not been evaluated in patients with **heart failure.** METHODS: Thalidomide was assessed in preclinical and clinical studies. First, isolated cardiac myocytes were pretreated with thalidomide or thalidomide analogues, and TNF production was assessed after lipopolysaccharide (**LPS**) provocation. Second, to determine the safety and potential efficacy of thalidomide, an open-label dose escalation safety study was conducted in seven patients with advanced **heart failure.** RESULTS: Thalidomide and thalidomide analogues inhibited **LPS**-induced TNF biosynthesis in cardiac myocytes in a dose-dependent manner. Thalidomide analogues had a greater inhibitory effect on TNF production than did thalidomide. In patients with advanced HF, thalidomide was safe and potentially effective when used at lower doses. However, dose-limiting toxicity was observed in two patients. There was a significant increase in the 6-minute walk distance and a trend toward improvement in left ventricular ejection fraction and quality of life after 12 weeks of maintenance therapy with thalidomide. CONCLUSIONS: Taken together these results suggest that thalidomide or its derivatives may be useful in selected patients with HF. This potential needs to be studied in larger clinical trials.

L13 ANSWER 17 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:382383 The Genuine Article (R) Number: 670GH. Interleukin-1 increases fibronectin production by cultured rat cardiac fibroblasts. Fernandez L; Mosquera J A (Reprint). Apartado Postal 1151, Maracaibo 4001A, Venezuela (Reprint); Univ Zulia, Inst Invest Clin Dr Amer Negrette, Fac Med, Maracaibo, Venezuela; Univ Zulia, Ctr Cirugia Expt, Maracaibo, Venezuela. PATHOBIOLOGY (OCT-DEC 2002) Vol. 70, No. 4, pp. 191-196. Publisher: KARGER . ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. ISSN: 1015-2008. Pub. country: Venezuela. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objectives: There is evidence of monocyte/macrophage infiltration and increased interleukin (IL)-1 expression, along with increased extracellular matrix (ECM) and fibrosis in the myocardial interstitium, during the course of parasitic, viral and idiopathic myocarditis. The aim of this study was to determine the effect of human and rat IL-1 on the production of fibronectin (FN) by rat cardiac fibroblast cultures. Methods:To test the role of IL-1 in the production of ECM, we determined the FN content in supernatants of rat myocardial fibroblast cultures incubated for 72 h with different doses of human recombinant IL-1 P or with supernatants from lipopolysaccharide (**LPS**)-stimulated rat macrophage cultures. The content of soluble FN was determined by ELISA. In addition, IL-1beta transcription was also investigated in controls and human recombinant IL-1beta-treated fibroblast cultures. Results:There was a significant, dose-dependent FN-stimulatory effect of recombinant human IL-1beta and **LPS**-stimulated macrophage-conditioned medium when they were used to stimulate fibroblast cultures. The stimulatory effect on FN production was found to be diminished after **treatment** of macrophage supernatants with an antibody against rat IL-1. Increased transcription of IL-1beta was found in human recombinant IL-1beta-treated

cardiac fibroblasts. Conclusion: Our data suggest that the FN-stimulatory effect of IL-1 on cardiac fibroblasts could be responsible, in part, for interstitial ECM accumulation during the course of myocarditis. Copyright (C) 2003 S. Karger AG, Basel.

L13 ANSWER 18 OF 46 MEDLINE on STN DUPLICATE 5
2002092665. PubMed ID: 11744024. Endotoxin induces desensitization of cardiac endothelin-1 receptor signaling by increased expression of RGS4 and RGS16. Patten Monica; Bunemann Jan; Thoma Bryan; Kramer Elisabeth; Thoenes Martin; Stube Sabine; Mittmann Clemens; Wieland Thomas. (Medizinische Klinik, Abteilung fur Kardiologie, Universitats-Krankenhaus Hamburg Eppendorf, Martinistr. 52, 20246 Hamburg, FRG.. patten@uke.uni-hamburg.de) . Cardiovascular research, (2002 Jan) 53 (1) 156-64. Journal code: 0077427. ISSN: 0008-6363. Pub. country: Netherlands. Language: English.

AB OBJECTIVE: Endotoxin (**LPS**)-induced acute cardiac failure during sepsis is associated with alterations in G protein mediated signal transduction. We therefore examined the expression of the G proteins G(i), G(q), and G(s) and of four 'regulators of G protein signaling' (RGS) proteins, RGS1, RGS4, RGS5, and RGS16 in rat hearts. METHODS: For in vivo experiments, Wistar rats were treated with 600 microg/day E. coli **LPS**, intravenously) and hearts were excised after 6, 24 and 72 h. Cultured neonatal rat cardiomyocytes were treated with 4 microg/ml **LPS** for 24 and 72 h. Isolated membrane proteins were used for Western blot analysis and for evaluation of phospholipase C (PLC) activity. RGS16 mRNA was detected by RNAse protection. RESULTS: **LPS** induced G(i) protein 1.4-fold 72 h after in vivo administration of **LPS**, whereas expression of G(s) and G(q) was unaltered. After 6 h of **LPS treatment**, RGS16 mRNA was transiently up-regulated 3.7-fold, followed by transient protein induction (24 h: 2.5-fold; 72 h: 1.5-fold). Similarly, RGS4 protein was transiently induced (24 h: 3.1-fold; 72 h: 1.5-fold), whereas expression of RGS1 and RGS5 was not altered. Similar to the **LPS**-treated rat hearts, RGS16 expression was transiently induced by **LPS** in cultured neonatal rat cardiomyocytes (24 h: 1.6-fold, 72 h: 0.9-fold). To determine the functional consequences of the RGS protein induction phospholipase C (PLC) activity was analyzed in membranes obtained from solvent and **LPS**-treated hearts. Basal and endothelin-1-stimulated PLC activity was transiently repressed by **LPS** with a maximum after 24 h although no apparent changes in PLCbeta1 or endothelin receptor expression could be detected. CONCLUSION: These data suggest that the rapid up-regulation of cardiac RGS4 and RGS16 is associated with a desensitization of endothelin-1 receptor signaling. Up-regulation of these RGS proteins may thus be involved in the early onset of cardiac failure during sepsis.

L13 ANSWER 19 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2001176141 EMBASE Effects of soluble TNF receptor **treatment** on lipopolysaccharide-induced myocardial cytokine expression. Kadokami T.; McTiernan C.F.; Kubota T.; Frye C.S.; Bounoutas G.S.; Robbins P.D.; Watkins S.C.; Feldman A.M.. A.M. Feldman, Cardiovasc. Inst. UPMC Hlth. Syst., 200 Lothrop S., S 572 Scaife Hall, Pittsburgh, PA 15213, United States. feldmanam@msx.upmc.edu. American Journal of Physiology - Heart and Circulatory Physiology 280/5 49-5 (H2281-H2291) 2001.
Refs: 60.
ISSN: 0363-6135. CODEN: AJPPDI. Pub. Country: United States. Language: English. Summary Language: English.

AB Tumor necrosis factor (TNF)-α plays a key role in the pathogenesis of septic shock syndrome, and myocardial TNF-α expression may contribute to this pathophysiology. We examined the myocardial expression of TNF-α-related cytokines and chemokines in mice exposed to lipopolysaccharide (**LPS**) and tested the effects of anti-TNF therapy on myocardial cytokine expression. Cytokine mRNA levels were measured by RNase protection assay, and protein levels in the plasma and

myocardium were assessed by enzyme-linked immunosorbent assays. **LPS** (4 μg/g body wt ip) induced marked cytokine expression, including TNF-α, interleukin (IL)-1β, IL-6, and monocyte chemotactic protein (MCP)-1, in both the plasma and myocardium. Pretreatment with adenovirus-mediated TNF receptor fusion protein (AdTNFR1; 10(9) plaque-forming units iv) decreased plasma cytokine levels. In contrast, whereas myocardial IL-1β expression was also suppressed, expression of IL-6 and MCP-1 was not inhibited by AdTNFR1. In summary, anti-TNF **treatment** differentially altered the cytokine expression in the plasma and myocardium during endotoxemia. Inability to block myocardial expression of IL-6 and MCP-1 suggests a possible mechanism for the failure of anti-TNF therapies in the **treatment** of endotoxin shock.

L13 ANSWER 20 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:351619 The Genuine Article (R) Number: 426CF. Wogonin, baicalin, and baicalein inhibition of inducible nitric oxide synthase and cyclooxygenase-2 gene expressions induced by nitric oxide synthase inhibitors and lipopolysaccharide. Chen Y C; Shen S C; Chen L G; Lee T J F; Yang L L (Reprint). Taipei Med Univ, Grad Inst Pharmacognosy Sci, 250 Wu Hsing St, Taipei, Taiwan (Reprint); Taipei Med Univ, Grad Inst Pharmacognosy Sci, Taipei, Taiwan; Taipei Med Univ, Sch Med, Dept Dermatol, Taipei, Taiwan; So Illinois Univ, Sch Med, Dept Pharmacol, Springfield, IL 62794 USA; Natl Chiayi Univ, Life Sci Coll, Grad Inst Biotechnol, Chiayi, Taiwan. BIOCHEMICAL PHARMACOLOGY (1 JUN 2001) Vol. 61, No. 11, pp. 1417-1427. Publisher: PERGAMON-ELSEVIER SCIENCE LTD. THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND. ISSN: 0006-2952. Pub. country: Taiwan; USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We previously reported that oroxylin A, a polyphenolic compound, was a potent inhibitor of lipopolysaccharide (**LPS**)-induced expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). In the present study, three oroxylin A structurally related polyphenols isolated from the Chinese herb Huang Qui, namely baicalin, baicalein, and wogonin, were examined for their effects on **LPS**-induced nitric oxide (NO) production and iNOS and COX-2 gene expressions in RAW 264.7 macrophages. The results indicated that these three polyphenolic compounds inhibited **LPS**-induced NO production in a concentration-dependent manner without a notable cytotoxic effect on these cells. The decrease in NO production was in parallel with the inhibition by these polyphenolic compounds of **LPS**-induced iNOS gene expression. However, these three compounds did not directly affect iNOS enzyme activity. In addition, wogonin, but not baicalin or baicalein, inhibited **LPS**-induced prostaglandin E, (PGE,) production and COX-2 gene expression without affecting COX-2 enzyme activity. Furthermore, N-nitro-L-arginine (NLA) and N-nitro-L-arginine methyl ester (L-NAME) pretreatment enhanced **LPS** -induced iNOS (but not COX-2) protein expression, which was inhibited by these three polyphenolic compounds. Wogonin, but not baicalin or baicalein, similarly inhibited PGE, production and COX-2 protein expression in NLA/**LPS** or L-NAME/**LPS**-co-treated RAW 264.7 cells. These results indicated that co-**treatment** with NOS inhibitors and polyphenolic compounds such as wogonin effectively blocks acute production of NO and, at the same time, inhibits expression of iNOS and COX-2 genes.

L13 ANSWER 21 OF 46 MEDLINE on STN DUPLICATE 6
2001572935. PubMed ID: 11680626. Endotoxin and cytokines alter contractile protein expression in cardiac myocytes in vivo. Patten M; Kramer E; Bunemann J; Wenck C; Thoenes M; Wieland T; Long C. (Medizinische Klinik, Abteilung fur Kardiologie, Universitats-Krankenhaus Hamburg Eppendorf, Hamburg, Germany.. patten@uke.uni-hamburg.de) . Pflugers Archiv : European journal of physiology, (2001 Sep) 442 (6) 920-7. Journal code: 0154720. ISSN: 0031-6768. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB Release of bacterial endotoxin and cytokines induce cardiac failure during

sepsis. We investigated the direct effects of E. coli endotoxin (lipopolysaccharide, **LPS**) and cytokines induced by **LPS** on the cardiac myocyte gene program. For in vivo-experiments adult Wistar rats were given 600 microg/day **LPS** i.v. for 24 h or 7 days. In addition, cultured adult rat cardiac myocytes were treated with **LPS**, interleukin-1beta (IL-1beta), tumour necrosis factor-alpha (TNFalpha), interferon-gamma (IFNgamma) or IL-6 for 24 h. mRNA expression was evaluated for cardiac-alpha-actin (cAct), skeletal-alpha-actin (skAct), beta- and alpha-myosin heavy chain (MHC). **LPS** induced betaMHC-mRNA 3.6-fold and repressed alphaMHC 2.7-fold and cAct 2.5-fold after 24 h in vivo. Up-regulation of betaMHC (3-fold) and repression of cAct (2.5-fold) were still observed after 7 days **LPS** infusion, whereas alphaMHC-mRNA levels had returned to normal. At the protein level, increased expression of betaMHC by **LPS treatment** occurred already after 24 h and was maintained thereafter. **LPS** had no influence on skAct-mRNA. Similar changes in contractile protein mRNA expression were observed in **LPS**-treated cardiomyocytes in culture, whereas the tested cytokines either activated (IL-1beta, IFNgamma) or repressed (TNFalpha, IL-6) both MHC-isoforms and cAct. In conclusion, **LPS** and proinflammatory cytokines induce changes in contractile protein expression that may contribute to the acute **heart failure** observed during endotoxaemia.

L13 ANSWER 22 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
2001:530545 Document No. 136:165084 Effect of cytokine-induced nitric oxide and peroxynitrite on cultured rat cardiac myocytes. Keira, Natsuya (Second Dep. Medicine, Kyoto Prefectural Univ. Med., Japan). Kyoto-furitsu Ika Daigaku Zasshi, 110(6), 499-512 (Japanese) 2001. CODEN: KFIZAO. ISSN: 0023-6012. Publisher: Kyoto-fu Igaku Shinkokai.

AB To clarify the role of nitric oxide (NO) in cytokine-mediated myocardial injury, the present study was designed to examine the combined effect of cytokines (IL-1β + interferon-γ) and lipopolysaccharide (**LPS**) on cardiac myocytes. Primary culture of rat neonatal cardiac myocytes was prepared, and NO-2/NO-3 (NOx) in the culture media was measured. **Treatment** with cytokines for 48 h resulted in a marked increase in NOx and creatine kinase (CK) and a significant decrease in cellular ATP. Cell death did not involve apoptosis but necrosis as determined by histochem. methods. NO synthase (NOS) inhibitors significantly prevented these metabolic changes and CK release. Uric acid (UA) and L-cysteine (L-Cys), which is known to scavenge peroxynitrite, also significantly attenuated CK release, although they affected neither NOx production nor reduction of cellular ATP. Immunohistochem. examination disclosed that cytokines-stimulation resulted in pos. nitrotyrosine staining in the myocytes, and that UA abolished the nitrotyrosine staining but had no effect on inducible NOS (iNOS) protein staining in the myocytes. The data suggest that the NO produced by iNOS in the myocytes is attributable to lethal myocardial damage, through the formation of peroxynitrite. These findings may help explain the pathogenesis of myocardial degeneration and impaired function in **heart failure.**

L13 ANSWER 23 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:242294 The Genuine Article (R) Number: 409BT. Ace-inhibition with quinapril modulates the nitric oxide pathway in normotensive rats. Bachetti T; Comini L; Pasini E; Cargnoni A; Curello S; Ferrari R (Reprint) . Univ Ferrara, Osped S Anna, Nuove Clin, Corso Giovecca 203, I-44100 Ferrara, Italy (Reprint); Univ Ferrara, Chair Cardiol, I-44100 Ferrara, Italy; Spedali Civili, Div Cardiol, I-25125 Brescia, Italy; IRCCS, Cardiovasc Pathophysiol Res Ctr, Salvatore Maugeri Fdn, Gussago, Italy. JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY (MAR 2001) Vol. 33, No. 3, pp. 395-403. Publisher: ACADEMIC PRESS LTD. 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND. ISSN: 0022-2828. Pub. country: Italy. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Angiotensin-converting enzyme (ACE) inhibitors exert some cardiovascular benefits by improving endothelial function. We evaluated

the effects of chronic **treatment** with quinapril (Q) on the (L)-arginine/nitric oxide (NO) pathway in normotensive rats under baseline and inflammatory conditions. The role of bradykinin was also investigated. The animals received for 1 week either the ACE-inhibitor Q (1 and 10 mg/kg/day). the B-2, receptor antagonist HOE 140, Q + HOE 140, or no drug. At the end of chronic **treatment**, rats underwent either a 6-h placebo or an E. coli endotoxin challenge. The following measurements were made: (i) endothelial and inducible NO synthase (eNOS and iNOS) protein expression: (ii) eNOS/iNOS activity; (iii) serum levels of nitrite/ nitrate and tumour necrosis factor (TNF)-alpha; (iv) NO in the expired air (eNO). Q increased baseline aortic eNOS protein expression (up to 99%, P<0.001) and activity ((L)-citrulline synthesis up to 94%. P<0.01; serum nitrite/ nitrate up to 55%, P<0.05). HOE 140 partially reversed Q-induced upregulation of eNOS (P<0.05). Moreover, Q counteracted **LPS** effects, i.e. increased the impaired eNOS pathway and limited iNOS induction (up to 94 and 24%, respectively), and reduced the increased nitrite/nitrate and TNF-alpha serum levels as well as eNO (up to 25, 38 and 28%, respectively. P<0.01 for all comparisons). HOE 140 did not influence Q effects on iNOS during endotoxaemia. In conclusion, in (patho)physiological conditions in rats, Q up-regulated eNOS with a bradykinin-mediated mechanism. while downregulated iNOS with a possible TNF-<alpha>-mediated mechanism. (C) 2001 Academic Press.

L13 ANSWER 24 OF 46 EMBASE
on STN

2001087660 EMBASE Protective effects of yangambin on cardiovascular hyporeactivity to catecholamines in rats with endotoxin-induced shock.

Araujo C.V.; Barbosa-Filho J.M.; Cordeiro R.S.B.; Tibirica E.. E. Tibirica, Depto. de Fisiologia/Farmacodinamica, Instituto Oswaldo Cruz, FIOCRUZ, Av. Brasil 4365-Manguinhos, 21045-900 Rio de Janeiro, RJ, Brazil. etibi@ioc.fiocruz.br. Naunyn-Schmiedeberg's Archives of Pharmacology 363/3 (267-275) 2001.
Refs: 48.
ISSN: 0028-1298. CODEN: NSAPCC. Pub. Country: Germany. Language: English. Summary Language: English.

AB The protective effects of a new, selective, plant-derived platelet-activating factor (PAF) antagonist, yangambin, on the cardiovascular alterations and mortality due to endotoxic shock were investigated in anaesthetized rats. We also studied the involvement of PAF in the induction of the vascular and cardiac hyporesponsiveness to adrenergic stimulation observed during endotoxaemia. The animals were sensitized to the lethal effects of Escherichia coli lipopolysaccharide (**LPS**) with D(+)-galactosamine (50 mg/kg, i.v.) 15 min before **LPS** injection. **LPS** (3 mg/kg, i.v.) induced a progressive and marked decrease in mean arterial blood pressure from 85±4 to 30±3 mmHg and a reduction of cardiac output (CO) from 180±7 to 37±3 ml/min (120 min) accompanied by a maintenance of systemic vascular resistance, suggesting that cardiovascular collapse resulted mainly from myocardial depression. The maximum pressor responses to noradrenaline (0.3-3.0 μg/kg, i.v.) fell from 72±9 (control) to 5±1 mmHg (**LPS**) while the CO responses decreased from 81±5 to 8±3 ml/min. Pre-**treatment** with yangambin (30 mg/kg, i.v.) or with WEB 2086 (5 mg/kg, i.v.), a reference PAF receptor antagonist, completely prevented the **LPS**-induced cardiovascular collapse and abolished the sharp reductions of the arterial blood pressure and CO responses to noradrenaline observed during endotoxaemia. Post-**treatment** with yangambin 90 min after **LPS** administration did not reverse the arterial hypotension, cardiac failure or cardiovascular hyporesponsiveness to catecholamines. Finally, the acute (150 min) survival rates of endotoxic shock increased from 0% (**LPS** group) to 100% in the groups pretreated with either yangambin or WEB 2086. The long-term (7-day) survival also increased from 0% (**LPS** group) to 85% (yangambin pre-**treatment** group). In conclusion, these data suggest a role for PAF in the pathogenesis of endotoxin-induced vascular and cardiac hyporesponsiveness to catecholamines and confirm its involvement in the

complex cascade of multiple mediators released during endotoxic/septic shock. Yangambin proved to be an effective pharmacological agent against cardiovascular collapse and mortality in endotoxin shock.

L13 ANSWER 25 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:319298 The Genuine Article (R) Number: 420AA. Role of endothelin-1/endothelin receptor system in endotoxic shock rats. Ishimaru S; Shichiri M; Mineshita S; Hirata Y (Reprint). Tokyo Med & Dent Univ, Dept Clin & Mol Endocrinol, Grad Sch, Bunkyo Ku, 1-5-45 Yushima, Tokyo 1138519, Japan (Reprint); Tokyo Med & Dent Univ, Dept Clin & Mol Endocrinol, Grad Sch, Bunkyo Ku, Tokyo 1138519, Japan; Tokyo Med & Dent Univ, Med Res Inst, Dept Prevent Med, Tokyo, Japan. HYPERTENSION RESEARCH (MAR 2001) Vol. 24, No. 2, pp. 119-126. Publisher: JAPANESE SOC HYPERTENSION CENT ACADEMIC SOC, PUBL OFFICE. OSAKA, 14TH FL, SENRI LIFE SCI CENTER BLDG, 4-2 SHINSENRI- HIGASHI-MACHI 1 CHOME, TOYONAKA, 565-0082, JAPAN. ISSN: 0916-9636. Pub. country: Japan. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Endothelin (ET)-1, a potent vasoconstrictor peptide derived from the endothelium, is markedly increased in endotoxic shock, although the pathophysiological role of ET-1 under septic conditions remains obscure. To delineate the role of ET-1 and its receptor subtype in endotoxic shock, we here attempted to determine the changes of circulating levels of ET-1 and its biosynthetic intermediate big ET-I in endotoxic shock rats, to evaluate the gene expression of ET-1 as well as the ET-1 receptor subtypes (ETA and ETB) in the heart, lung and liver, and to study the effects of ET receptor antagonists on systemic arterial blood pressure, heart rate and survival rate, Administration of bacterial lipopolysaccharide (**LPS**) caused profound hypotension, increased heart rate and death, and these effects were blocked by a nonselective ETA/ETB receptor antagonist (TAK044), but not by an ETA selective antagonist (BQ123), Administration of exogenous ET-1 caused a profound presser response in control rats, but not in the **LPS**-pretreated rats. Injection of **LPS** caused marked elevation of plasma levels of both ET-1 and big ET-1, which were not affected by **treatment** with either ET receptor antagonist. Administration of **LPS** caused up-regulation of ET-1 and ETB receptor mRNA in the heart, whereas ETA receptor mRNA was markedly down-regulated in the heart, lung and liver. These data suggest differential gene regulation of ET-1 and its receptor subtypes in various organs from endotoxic shock rats, and that nonselective ETA/ETB receptor antagonist, but not ETA receptor antagonist, ameliorates endotoxin-induced hypotension and death.

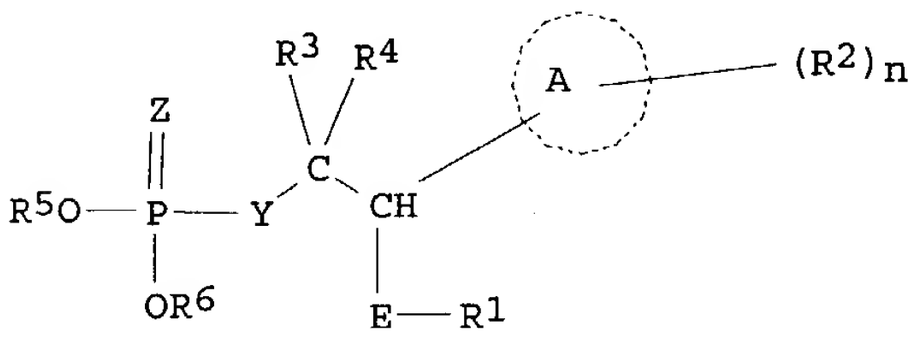
L13 ANSWER 26 OF 46 MEDLINE on STN DUPLICATE 7
2001223234. PubMed ID: 11192310. Comparison of tumor necrosis factor-alpha effect on the expression of iNOS in macrophage and cardiac myocytes. Sanders D B; Larson D F; Hunter K; Gorman M; Yang B. (Circulatory Sciences Graduate Perfusion Program, Sarver Heart Center, University of Arizona, Tucson 85724, USA.) Perfusion, (2001 Jan) 16 (1) 67-74. Journal code: 8700166. ISSN: 0267-6591. Pub. country: England: United Kingdom. Language: English.

AB Proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-alpha), are elevated during cardiopulmonary bypass (CPB), **heart failure**, and inflammatory cardiac and systemic diseases. Elevated TNF-alpha has been linked to diminished cardiac function, decreased systemic vascular resistance, as well as renal and pulmonary dysfunction. It is understood that myocardial tissues can express TNF-alpha, which results in the induction of inducible nitric oxide synthase (iNOS) leading to a significant decline in cardiac function and other direct effects. The hypothesis of this study was to determine if TNF-alpha would stimulate iNOS and its product nitric oxide (NO) similarly in immortalized macrophage and cardiac myocytes. Cultured macrophages (RAW 264.7) and cardiac myocytes (HL-1) were placed into two **treatment** groups and a control. The **treatments** included: (1) TNF-alpha and lipopolysaccharide (**LPS**); and (2) **LPS**, TNF-alpha, interleukin-1beta (IL-1beta) and interferon-gamma

(IFN-gamma) incubated for 8 h. The macrophage expression of iNOS increased by 365% ($p < 0.01$) and its product, NO, increased proportionally. The expression of iNOS in the cardiac myocyte did not increase with TNF-alpha and **LPS.** However, with the addition of IFN-alpha and IL-1beta iNOS increased to 140% of control ($p < 0.05$). Myocyte cGMP and NO did not increase significantly with TNF-alpha **treatment.** This study suggests that HL-1 myocyte iNOS cannot be induced by TNF-alpha, unlike macrophage iNOS. Furthermore, the resultant cardiac dysfunction, secondary to proinflammatory cytokines effects, is regulated via diverse pathways.

L13 ANSWER 27 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
2000:608753 Document No. 133:193275 Preparation of phosphoric acid derivatives as TNF-α production inhibitors. Matsui, Toshiaki; Ohmawari, Nagashige (Ono Pharmaceutical Co., Ltd., Japan). PCT Int. Appl. WO 2000050429 A1 20000831, 253 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP1005 20000222. PRIORITY: JP 1999-44840 19990223; JP 1999-283104 19991004.

GI



I

AB The title compds. I [R1 = alkyl, etc.; ring A = heterocyclic ring, etc.; R2 = NR7CO, etc.; R7 = H, alkyl; R3, R4 = H, alkyl, etc.; further details on R3 and R4 are given; n = 0 or n ≥ 1; R5, R6 = H, alkyl, Ph, etc.; E = NR7CO, etc.; Y, Z = O, S; provisos are given] are prepared I are useful as preventives and/or remedies for rheumatoid arthritis, ulcerative colitis, Crohn's disease, hepatitis, sepsis, hemorrhagic shock, multiple sclerosis, brain infarction, diabetes, interstitial pneumonia, uveitis, pain, glomerulonephritis, HIV-associated diseases, cachexia, myocardial infarction, chronic **heart failure**, Hansen's disease, infection, etc. (2R)-2-Phenyl-2-(N-octanoylamino)ethyl phosphate disodium salt showed ED50 of 2.6 mg/kg against TNF-α production in mice treated with **LPS.** A formulation is given.

L13 ANSWER 28 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
2000:513526 Document No. 133:134187 Method of treating chronic cardiac disease. Giroir, Brett P.; Scannon, Patrick J. (Xoma Technology Ltd., USA; Board of Regents, the University of Texas System). PCT Int. Appl. WO 2000043028 A2 20000727, 36 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US1515 20000121. PRIORITY: US 1999-PV116736 19990122.

AB New therapeutic uses for bactericidal/permeability-increasing (BPI) protein products that involve **treatment** of chronic cardiac disease. The chronic cardiac diseases include chronic congestive **heart failure**, cardiomyopathy, and congenital heart defect. The patients with chronic cardiac disease exhibit elevated level of circulating **LPS** and LBP.

L13 ANSWER 29 OF 46 MEDLINE on STN DUPLICATE 8
2001012623. PubMed ID: 11009565. Peroxisome proliferator-activated receptor activators inhibit lipopolysaccharide-induced tumor necrosis factor-alpha expression in neonatal rat cardiac myocytes. Takano H; Nagai T; Asakawa M; Toyozaki T; Oka T; Komuro I; Saito T; Masuda Y. (Third Department of Internal Medicine, Chiba University School of Medicine, Japan.. htakano-cib@umin.ac.jp) . Circulation research, (2000 Sep 29) 87 (7) 596-602. Journal code: 0047103. ISSN: 1524-4571. Pub. country: United States. Language: English.

AB Peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to the nuclear receptor superfamily. Recently, PPAR activators have been shown to inhibit the production of proinflammatory cytokines in macrophages or vascular smooth muscle cells. It has been reported that tumor necrosis factor-alpha (TNF-alpha) expression is elevated in the failing heart and that TNF-alpha has a negative inotropic effect on cardiac myocytes. Therefore, we examined the effects of PPARalpha and PPARgamma activators on expression of TNF-alpha in neonatal rat cardiac myocytes. Northern blot analysis revealed expression of PPARalpha and PPARgamma mRNA in cardiac myocytes. Immunofluorescent staining demonstrated that both PPARalpha and PPARgamma were expressed in the nuclei of cells. When cardiac myocytes were transfected with PPAR responsive element (PPRE)-luciferase reporter plasmid, both PPARalpha and PPARgamma activators increased the promoter activity. Cardiomyocytes were stimulated with lipopolysaccharide (**LPS**), and the levels of TNF-alpha in the medium were measured by ELISA. After exposure to **LPS**, the levels of TNF-alpha significantly increased. However, pretreatment of myocytes with PPARalpha or PPARgamma activators decreased **LPS**-induced expression of TNF-alpha in the medium. Both PPARalpha and PPARgamma activators also inhibited **LPS**-induced increase in TNF-alpha mRNA in myocytes. In addition, electrophoretic mobility shift assays demonstrated that PPAR activators reduced **LPS**-induced nuclear factor-kappaB activation. These results suggest that both PPARalpha and PPARgamma activators inhibit cardiac expression of TNF-alpha in part by antagonizing nuclear factor-kappaB activity and that **treatment** with PPAR activators may lead to improvement in congestive **heart failure.**

L13 ANSWER 30 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:773558 The Genuine Article (R) Number: 362AB. Peroxisome proliferator-activated receptor activators inhibit lipopolysaccharide-induced turner necrosis factor-alpha expression in neonatal rat cardiac myocytes. Takano H (Reprint); Nagai T; Asakawa M; Toyozaki T; Oka T; Komuro I; Saito T; Masuda Y. CHIBA UNIV, SCH MED, DEPT INTERNAL MED 3, CHUO KU, 1-8-1 INOHANA, CHIBA 2608670, JAPAN (Reprint); UNIV TOKYO, GRAD SCH MED, DEPT CARDIOVASC MED, TOKYO, JAPAN. CIRCULATION RESEARCH (29 SEP 2000) Vol. 87, No. 7, pp. 596-602. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621. ISSN: 0009-7330. Pub. country: JAPAN. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to the nuclear receptor superfamily. Recently, PPAR activators have been shown to inhibit the production of proinflammatory cytokines in macrophages or vascular smooth muscle cells. It has been reported that tumor necrosis factor-alpha (TNF-alpha) expression is elevated in the failing heart and that TNF-alpha has a negative inotropic effect on cardiac myocytes. Therefore, we examined the effects of PPAR alpha and PPAR gamma activators on expression of TNF-alpha in neonatal rat cardiac myocytes. Northern blot analysis revealed expression of PPAR alpha

and PPAR gamma mRNA in cardiac myocytes. Immunofluorescent staining demonstrated that both PPAR alpha and PPAR gamma were expressed in the nuclei of cells. When cardiac myocytes were transfected with PPAR responsive element (PPRE)-luciferase reporter plasmid, both PPAR alpha and PPAR gamma activators increased the promoter activity. Cardiomyocytes were stimulated with Lipopolysaccharide (**LPS**), and the levels of TNF-alpha in the medium were measured by ELISA. After exposure to **LPS**, the levels of TNF-alpha significantly increased. However, pretreatment of myocytes with PPAR alpha or PPAR gamma activators decreased **LPS**-induced expression of TNF-alpha in the medium. Both PPAR alpha and PPAR gamma activators also inhibited **LPS** -induced increase in TNF-alpha mRNA in myocytes. In addition, electrophoretic mobility shift assays demonstrated that PPAR activators reduced **LPS**-induced nuclear factor-kappa B activation. These results suggest that both PPAR alpha and PPAR gamma activators inhibit cardiac expression of TNF-alpha in part by antagonizing nuclear factor-kappa B activity and that **treatment** with PPAR activators may lead to improvement in congestive **heart failure.**

L13 ANSWER 31 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2000275715 EMBASE Analysis of heart rate variability and late potentials (LP) after left ventricular aneurysmectomy - Preliminary communication.
Straburzynska-Migaj E.; Sarnowski W.; Katarzynski S.; Wachowiak H.B.; Lacinski M.; Ochotny R.. Dr. E. Straburzynska-Migaj, Institute of Cardiology, University of Medical Sciences, ul. Dluga 1/2, 61-848 Poznan, Poland. Cor Europaeum - European Journal of Cardiac Interventions 8/3 (100-102) 2000.
Refs: 12.
ISSN: 0939-8147. CODEN: COEUF3. Pub. Country: Germany. Language: English. Summary Language: English.

AB **Heart failure** and ventricular arrhythmia resistant to medical **treatment** are indications for surgical resection of postinfarction aneurysm. Excision is thought to eliminate the substrate of arrhythmia, but occasionally remaining scar is the source of electrical instability. We studied the influence of aneurysmectomy on heart rate variability and the incidence of ventricular arrhythmia, and late potentials. Material and methods: We investigated 12 patients after CABG and excision/plication of the aneurysm of left ventricle. Age ranged from 41 to 71 years (mean 56 ± 10). In patients of group 1 (6 M and 2 W) aneurysms of apex and anterior wall were excised. In patients of group 2 (4 M) only aneurysms of the postero-inferior wall were excised. Follow-up time was 18 ± 9 months. There was no significant difference between the groups in terms of left ventricular function assessed as ejection fraction using echocardiography (43 ± 9% in group 1 vs 47 ± 8% in group 2). All the patients had ambulatory 24 hours ECG monitoring with heart rate variability (HRV) assessment, and signal averaged ECG (SAECG) with late potentials (LP) analysis. Results: Two patients (50%) of group 2 and one patient (12.5%) of group 1 had complex ventricular arrhythmia. There was no essential difference between the groups in terms of HVR parameters. In SAECG 1 patient (12.5%) of group 1 and 3 patients (75%) of group 2 had positive **LPs** (p = 0.06). There were also significant differences in 2 of 3 SAECG parameters: Low Amplitude Signals (AS) and Root mean square (RMS) between the two groups, advantageous in group 1. Conclusions: There is probably a lower incidence of ventricular arrhythmias and **LPs** after excision of the apical and anterior wall aneurysm than of the postero-inferior wall aneurysm.

L13 ANSWER 32 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

1999:437776 The Genuine Article (R) Number: 202TG. Endotoxin and immune activation in chronic **heart failure**: a prospective cohort study. Niebauer J; Volk H D; Kemp M; Dominguez M; Schumann R R; Rauchhaus M; PooleWilson P A; Coats A J S; Anker S D (Reprint). NATL HEART & LUNG INST, IMPERIAL COLL SCH MED, DOVEHOUSE ST, LONDON SW3 6LY, ENGLAND (Reprint); NATL HEART & LUNG INST, IMPERIAL COLL SCH MED, LONDON SW3 6LY,

ENGLAND; UNIV LEIPZIG, HERZZENTRUM, LEIPZIG, GERMANY; UNIV KLINIKUM CHARITE, INST MED IMMUNOL, BERLIN, GERMANY; HAREFIELD HOSP, HEART SCI CTR, HAREFIELD, MIDDX, ENGLAND; UNIV KLINIKUM CHARITE, INST MIKROBIOL & HYG, BERLIN, GERMANY; MAX DELBRUCK CTR MOL MED, FRANZ VOLHARD KLIN, BERLIN, GERMANY. LANCET (29 MAY 1999) Vol. 353, No. 9167, pp. 1838-1842. Publisher: LANCET LTD. 42 BEDFORD SQUARE, LONDON WC1B 3SL, ENGLAND. ISSN: 0140-6736. Pub. country: ENGLAND; GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background. Immune activation in patients with chronic **heart failure** may be secondary to endotoxin (lipopolysaccharide) action. We investigated the hypothesis that altered gut permeability with bacterial translocation and endotoxaemia would be increased in patients with oedema secondary to congestive **heart failure.**

Methods. We compared 20 patients who had chronic **heart failure** with recent-onset peripheral oedema (mean age 64 years [SD 10], New York Heart Association [NYHA] class 3.3 [0.7]), 20 stable non-oedematous patients with chronic **heart failure** (mean age 63 years [19], NYHA class 2.6 [0.7]), and 14 healthy volunteers (mean age 55 years [16]). Biochemical markers of endotoxaemia, inflammation, and immune activation were measured. Ten patients were studied within 1 week of complete resolution of oedema. Five patients survived longer than 6 months and were restudied again after remaining free of oedema for more than 3 months.

Findings. Mean endotoxin concentrations were higher in oedematous patients with chronic **heart failure** than in stable patients with chronic **heart failure** (0.74 [SD 0.45] vs 0.37 EU/mL [0.23], p = 0.0009) and controls (0.46 EU/mL [0.21], p = 0.02). Oedematous patients had the highest concentrations of several cytokines. After short-term diuretic **treatment**, endotoxin concentrations decreased from 0.84 EU/mL [0.49] to 0.45 EU/mL [0.21], p < 0.05) but cytokines remained raised. After freedom of oedema for more than 3 months after oedema resolved, endotoxin concentrations remained unchanged from the previous visit (0.49 EU/mL [0.06], p = 0.45).

Interpretation. Raised concentrations of endotoxin and cytokines are found in patients with chronic **heart failure** during acute oedematous exacerbation. Intensified diuretic **treatment** can normalise endotoxin concentrations. Our preliminary findings suggest that endotoxin may trigger immune activation in patients with chronic **heart failure** during oedematous episodes.

L13 ANSWER 33 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:871285 The Genuine Article (R) Number: 253ME. Transvenous parasympathetic cardiac nerve stimulation: An approach for stable sinus rate control. Schauerte P N; Scherlag B J (Reprint); Scherlag M A; Goli S; Jackman W; Lazzara R. UNIV OKLAHOMA, HLTH SCI CTR, DVA MED CTR, RES SERV 151F, 921 NE 13TH ST, OKLAHOMA CITY, OK 73104 (Reprint); UNIV OKLAHOMA, HLTH SCI CTR, DEPT INTERNAL MED, CARDIOVASC SECT, OKLAHOMA CITY, OK; DEPT VET AFFAIRS MED CTR, OKLAHOMA CITY, OK. JOURNAL OF CARDIOVASCULAR ELECTROPHYSIOLOGY (NOV 1999) Vol. 10, No. 11, pp. 1517-1524. Publisher: FUTURA PUBL CO. 135 BEDFORD RD, PO BOX 418, ARMONK, NY 10504-0418. ISSN: 1045-3873. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Introduction: Epicardial electrical stimulation of parasympathetic nerves innervating the sinus node has been shown to decrease sinus rate. We investigated whether intravascular parasympathetic cardiac nerve stimulation (IPS) can be achieved over a relatively long-term period to slow the supraventricular rate.

Methods and Results: Fifteen dogs were investigated. IFS was performed with rectangular stimuli (0.05-msec duration, 20 Hz) using a catheter with an expandable electrode basket. The catheter was positioned in the superior vena cava (SVC; n = 9) or right pulmonary artery (RPA; n = 6), The basket then was expanded to hold the catheter in place. Nonfluoroscopic identification of effective IFS sites was achieved within 5 minutes in the SVC, Increasing IFS voltage resulted in a graded response of supraventricular rate slowing. A 50% prolongation of the baseline

atrial cycle length was achieved with 28 V in the SVC (1,056 +/- 355 msec vs 489 +/- 154 msec; P < 0.001) and 25 V in the RPA (1,181 +/- 306 msec vs 518 +/- 138 msec; P < 0.01), The rate slowing started immediately after IFS onset, terminated abruptly after IFS cessation, and could be maintained over 10 hours. A rate slowing effect also was observed when the sinus rate was increased by isoproterenol (SVC: 304 +/- 8 msec/RPA: 341 +/- 9 msec with isoproterenol vs SVC: 635 +/- 12 msec with isoproterenol + **LPS** at 39 V/ RPA: 584 +/- 16 msec with isoproterenol + TPS at 38 V; n = 6).

Conclusion: IFS results in a significant supraventricular rate slowing that is stable over a relatively long period and may be applied to slow undesirable sinus tachycardia in acute ischemic syndromes or to counteract undesirable chronotropic effects of catecholamines during **treatment** of cardiogenic or septic shock and acute congestive **heart failure.**

L13 ANSWER 34 OF 46 MEDLINE on STN
1999190258. PubMed ID: 10091837. Effects of endotoxin on human myocardial contractility involvement of nitric oxide and peroxynitrite. Flesch M; Kilter H; Cremers B; Laufs U; Sudkamp M; Ortmann M; Muller F U; Bohm M. (Klinik III fur Innere Medizin, der Universitat zu Koln, Germany.. markus.flesch@medizin.uni-koeln.de) . Journal of the American College of Cardiology, (1999 Mar 15) 33 (4) 1062-70. Journal code: 8301365. ISSN: 0735-1097. Pub. country: United States. Language: English.

AB OBJECTIVES: This study examined the effects of endotoxin on cardiac contractility in human myocardium. BACKGROUND: In animal myocardium, endotoxin and cytokine **treatment** led to enhanced inducible nitric oxide synthase (iNOS) expression and contractile dysfunction. Effects in human myocardium are unknown. METHODS: Left ventricular myocardial preparations from failing (n = 18) and nonfailing (n = 5) human hearts were incubated for 6 and 12 h in tyrode solution or in tyrode plus lipopolysaccharides (**LPS**), with **LPS** plus N(G)-mono-methyl-L-arginine (L-NMMA), with **LPS** plus hemoglobin or with **LPS** plus the superoxide scavenger 4,5-dihydroxy-1,3-benzene disulfonic acid (Tiron). Force of contraction in response to isoprenaline (0.001 to 3 micromol/liter) was determined in electrically stimulated muscle preparations. The iNOS mRNA expression was examined by in situ hybridization and by polymerase chain reaction. The cyclic guanosine monophosphate (cGMP) levels were determined by radioimmunoassay. RESULTS: Isoprenaline concentration dependently increased force of contraction. Six and 12 hours of **LPS treatment** of failing myocardium decreased maximum inotropic response to isoprenaline by 54% (p = 0.009) and by 69% (p = 0.0023), respectively. In nonfailing myocardium, 12 h of **LPS treatment** decreased maximum inotropic effect of isoprenaline by 66% (p < 0.001). The **LPS** effects were attenuated by L-NMMA, hemoglobin and also Tiron. The iNOS mRNA was expressed in all **LPS**-treated preparations but also in most control myocardial preparations. In situ hybridization revealed iNOS expression within cardiac myocytes. There was no increase in myocardial cGMP content in response to endotoxin. CONCLUSIONS: Endotoxin exposure of human myocardium leads to a depression of cardiac contractility, which is mediated by enhanced iNOS activity and release of nitric oxide (NO). Consecutive reaction of NO with superoxide and formation of peroxynitrite may contribute to the decrease in force of contraction.

L13 ANSWER 35 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:503396 The Genuine Article (R) Number: 209PY. The effect of vesnarinone on TNF alpha production in human peripheral blood mononuclear cells and microglia: a preclinical study for the **treatment** of multiple sclerosis. Jiang H; Bielekova B; Okazaki H; ClarenceSmith K; Johnson K P; Bergey G; Martin R; DhibJalbut S (Reprint). UNIV MARYLAND HOSP, DEPT NEUROL, ROOM N4W46, 22 S GREENE ST, BALTIMORE, MD 21201 (Reprint); UNIV MARYLAND, DEPT NEUROL, BALTIMORE, MD 21201; NINCDS, NEUROIMMUNOL BRANCH, BETHESDA, MD 20842; OTSUKA PHARMACEUT CO LTD, TOKUSHIMA 7710192, JAPAN. JOURNAL OF NEUROIMMUNOLOGY (1 JUN 1999) Vol. 97, No. 1-2, pp. 134-145.

Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS . ISSN: 0165-5728. Pub. country: USA; JAPAN. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Vesnarinone (OPC-8212) is a synthetic quinolinone derivative with inotropic and immunomodulatory effects. Vesnarinone has been shown to inhibit tumor necrosis factor-alpha (TNF alpha) produced by mitogen stimulated macrophages. and to inhibit phosphodiesterase (PDE) type III in cardiac muscle. TNF alpha and interferon-gamma (IFN gamma) have been implicated in the pathogenesis of autoimmune diseases, and both cytokines are targets for therapeutic intervention. IFN gamma can enhance autoimmune disease through direct effects, and indirectly by priming macrophages to produce TNF alpha. In this study, we demonstrate that while vesnarinone enhances basal TNF alpha levels, it inhibits TNF alpha production in peripheral blood mononuclear cells from multiple sclerosis (MS) patients and healthy donors stimulated with lipopolysaccharide (**LPS**) or primed with IFN gamma and stimulated with suboptimal doses of **LPS** . In addition, vesnarinone inhibited TNF alpha production in primary adult human microglial cultures. However, in contrast to rolipram, another TNF alpha inhibiting agent, vesnarinone failed to inhibit TNF alpha production by myelin basic protein specific T-cell lines. As oral TNF inhibitors are currently being considered in the USA for clinical application in MS, the implications of our findings on the development of vesnruinone for **treatment** of hlS are discussed. (C) 1999 Elsevier Science B.V. All rights reserved.

L13 ANSWER 36 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:65114 The Genuine Article (R) Number: 155LC. **LPS**-Induced TNF-alpha release from and apoptosis in rat cardiomyocytes: Obligatory role for CD14 in mediating the **LPS** response. Comstock K L; Krown K A (Reprint); Page M T; Martin D; Ho P; Pedraza M; Castro E N; Nakajima N; Glembotski C C; Quintana P J E; Sabbadini R A. REES STEALY RES FDN, 2001 4TH AVE, SAN DIEGO, CA 92101 (Reprint); REES STEALY RES FDN, SAN DIEGO, CA 92101; SAN DIEGO STATE UNIV, DEPT BIOL, SAN DIEGO, CA 92182; SAN DIEGO STATE UNIV, GRAD SCH PUBL HLTH, SAN DIEGO, CA 92182. JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY (DEC 1998) Vol. 30, No. 12, pp. 2761-2775. Publisher: ACADEMIC PRESS LTD. 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND. ISSN: 0022-2828. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The bacterial endotoxin lipopolysaccharide (**LPS**) contributes to the cardiovascular collapse and death observed in patients with sepsis. Because **LPS** has such profound effects on cardiac performance, we speculate that direct effects of **LPS** could be demonstrated on cardiomyocytes in culture, and that these direct effects are mediated by the **LPS** receptor, CD14. Accordingly, in this study, we provide evidence for CD14-dependent cardiotoxic effects of **LPS** including the **LPS**-stimulated secretion of tumor necrosis factor alpha (TNF-alpha) from cardiomyocytes. TNF-alpha is an inflammatory cytokine which is renown for its negative inotropic effects on cardiac performance, but has not until recently been shown to be produced by cardiac cells. In this study, **LPS** was found to stimulate strongly in a dose-dependent manner the secretion of TNF-alpha from cultured adult rat cardiomyocytes. Further, **LPS**-induced TNF-alpha secretion was blocked by an inhibitor of TNF-alpha processing metallomatrix protease inhibitor (TAPI). Molecular and immulogical evidence demonstrated the presence of **LPS** receptors (CD14) on cardiomyocytes. Attenuated TNF-alpha secretion following PI-PLC **treatment** confirmed the functional importance of CD14 for **LPS**-mediated myocardial effects. Importantly, **LPS** also triggered apoptosis in cultured cardiomyocytes as quantified by single-cell gel electrophoresis of nuclei exhibiting DNA fragmentation patterns characteristic of apoptosis (i.e. cardiac comets). Apoptotic cell death was blocked by pre-incubation with the soluble TNF-alpha receptor fragment (TNFRII:Fc), suggesting that **LPS**-induced apoptosis was TNF-alpha-dependent and probably involved an autocrine function for the TNF-alpha whose secretion was under **LPS** control. The results of this study suggest that the

cardiodepressant effects of **LPS** are dependent on CD14 signaling and may not only be due to acute negative inotropic effects of TNE-alpha but also may be complicated by TNF-alpha-induced apoptotic cell death which effectively reduces the number of working myocardial cells. (C) 1998 Academic Press.

L13 ANSWER 37 OF 46 MEDLINE on STN DUPLICATE 9
1998315682. PubMed ID: 9618239. Cardiodepressant effects of interferon-gamma and endotoxin reversed by inhibition of NO synthase 2 in rat myocardium. Sun X; Delbridge L M; Dusting G J. (Department of Physiology, University of Melbourne, Parkville, Victoria, Australia.) Journal of molecular and cellular cardiology, (1998 May) 30 (5) 989-97. Journal code: 0262322. ISSN: 0022-2828. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Endogenous nitric oxide (NO) signalling pathways within the myocardium depress myocardial contractile function in septic shock and some cardiomyopathies. We have explored the role of NO synthases (NOSs) in mediating the cardiodepressant actions of interferon-gamma (IFN-gamma) and lipopolysaccaride (**LPS**) in rat papillary muscle. Muscles from the right ventricle were electrically stimulated (0.2 Hz) at 30 degrees C and isometric contraction monitored. Exposure to IFN-gamma and **LPS** for 15 h in vitro significantly decreased the peak tension (PT for IFN-gamma + **LPS**, from 0.13 +/- 0.03 to 0.07 +/- 0.02 g) and rate of tension development (dT/dt for IFN-gamma + **LPS**, from 1.78 +/- 0.36 to 1.17 +/- 0.28 g/s) compared to untreated controls, and this was prevented by dexamethasone (1 microM) and partly reversed by a non-specific NOS inhibitor, NG-nitro-L-arginine (NOLA, 30 microM). Likewise, the maximum inotropic response of the papillary muscles to isoprenaline (0.001-10 microM) decreased significantly after 15 h **treatment** with IFN-gamma and **LPS** (PT from 83 +/- 18 to 28 +/- 6%; +dT/dt from 83 +/- 12 to 31 +/- 7%; -dT/dt from 83 +/- 12 to 38 +/- 6%). Again, the depressant effects of IFN-gamma and **LPS** on inotropic responsiveness to isoprenaline were completely prevented by pretreatment with dexamethasone (1 microM), by a specific inhibitor of NOS2, mercaptoethylguanidine (MEG, 30 microM) and by NOLA. Whereas dexamethasone and NOLA protected against the attenuation of baseline contractions induced by **LPS** and IFN-gamma, MEG did not. Western blot analysis of cardiac myocytes showed that there was no constitutive expression of NOS2, but IFN-gamma and **LPS** induced expression of NOS2, and this was prevented by dexamethasone. Thus IFN-gamma, in the presence of **LPS**, reduced papillary muscle contraction and decreased responsiveness to beta-adrenoceptor stimulation through induction of NOS2 in the muscle. Increased NO production may contribute to the cardiac depression during septic shock and anti-cancer therapy with cytokines, and perhaps in **heart failure.**

L13 ANSWER 38 OF 46 EMBASE
on STN
1998286391 EMBASE TNF-α and myocardial depression in endotoxemic rats: Temporal discordance of an obligatory relationship. Meng X.; Ao L.; Meldrum D.R.; Cain B.S.; Shames B.D.; Selzman C.H.; Banerjee A.; Harken A.H.. X. Meng, Dept. of Surgery, Box C-320, Univ. of Colorado Health Sci. Ctr., 4200 East 9th Ave., Denver, CO 80262, United States. American Journal of Physiology - Regulatory Integrative and Comparative Physiology 275/2 44-2 (R502-R508) 1998.
Refs: 40.
ISSN: 0363-6119. CODEN: AJPRDO. Pub. Country: United States. Language: English. Summary Language: English.

AB Exogenous tumor necrosis factor-α (TNF-α) induces delayed myocardial depression in vivo but promotes rapid myocardial depression in vitro. The temporal relationship between endogenous TNF-α and endotoxemic myocardial depression is unclear, and the role of TNF-α in this myocardial disorder remains controversial. Using a rat model of endotoxemia not complicated by shock, we sought to determine 1) the temporal relationship of changes in circulating and myocardial TNF-α

with myocardial depression, 2) the influences of protein synthesis inhibition or immunosuppression on TNF-α production and myocardial depression, and 3) the influence of neutralization of TNF-α on myocardial depression. Rats were treated with lipopolysaccharide (**LPS**, 0.5 mg/kg ip). Circulating and myocardial TNF-α increased at 1 and 2 h, whereas myocardial contractility was depressed at 4 and 6 h. Pretreatment with cycloheximide or dexamethasone abolished the increase in circulating and myocardial TNF-α and preserved myocardial contractile function. Similarly, **treatment** with TNF binding protein immediately after **LPS** prevented myocardial depression. We conclude that endogenous TNF-α mediates delayed myocardial depression in endotoxemic rats and that inhibition of TNF-α production or neutralization of TNF-α preserves myocardial contractile function in endotoxemia.

L13 ANSWER 39 OF 46 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1998:247456 The Genuine Article (R) Number: ZC577. A therapeutic dosage of amlodipine prevents vascular hyporeactivity induced in rats by lipopolysaccharide. Salomone S; Morel N; Godfraind T (Reprint). UNIV CATHOLIQUE LOUVAIN, PHARMACOL LAB, FARL 5410, AVE HIPPOCRATE 54, B-1200 BRUSSELS, BELGIUM (Reprint); UNIV CATHOLIQUE LOUVAIN, PHARMACOL LAB, FARL 5410, B-1200 BRUSSELS, BELGIUM. NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY (MAR 1998) Vol. 357, No. 3, pp. 252-259. Publisher: SPRINGER VERLAG. 175 FIFTH AVE, NEW YORK, NY 10010. ISSN: 0028-1298. Pub. country: BELGIUM. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The aim of this work was to investigate whether **treatment** with the 1,4-dihydropyridine Ca2+ antagonist amlodipine could affect the vascular hyporesponsiveness induced by cytokines. Endotoxemia was induced by Salmonella typhosa lipopolysaccharide (**LPS**) injection (4 mg kg(-1), i.p.). In endothelium-denuded rings of thoracic aorta from untreated rats, contractile response to noradrenaline was decreased after **LPS** injection, this effect was partially overcome by the addition of N-omega-nitro-L-arginine (L-NNA, 100 mu M) into the bathing solution. In amlodipine-pretreated rats (15 mg kg(-1) day(-1), orally, for one week), the effect of **LPS** was lower than in untreated ones and it was completely reversed by L-NNA. The relaxation of the noradrenaline-induced tone evoked by L-arginine (10 mu M) in aortae of **LPS**-injected rats was reduced in amlodipine-pretreated rats. Amlodipine-**treatment** reduced both the **LPS**-induced Ca2+-indcpendent NOS activity in homogenates of heart and the expression of iNOS mRNA in aortae of **LPS**-injected rats. However, the vascular hyporeactivity induced by exposing aortae to interleukin-1 beta in vitro was not influenced by amlodipine (10 nM). Amlodipine (10 mu M) also did not affect the production of nitrite in primary aortic smooth muscle cell culture challenged by **LPS** although nitrite production in macrophage culture challenged with **LPS** was significantly inhibited.
The results show that rat pretreatment with amlodipine prevented the decrease of vascular responsiveness induced by **LPS**, an effect that may be at least paltry related to reduction of in vivo NOS induction. The weak effect of amlodipine on the in vitro NOS induction indicates that the protective action in endotoxemia did not result from a short term interaction with L-type Ca2+ channels in vascular smooth muscle. Alternative mechanisms are discussed.

L13 ANSWER 40 OF 46 MEDLINE on STN DUPLICATE 10
97459578. PubMed ID: 9315538. Modulation of cytokine production and protection against lethal endotoxemia by the cardiac glycoside ouabain. Matsumori A; Ono K; Nishio R; Igata H; Shioi T; Matsui S; Furukawa Y; Iwasaki A; Nose Y; Sasayama S. (Department of Cardiovascular Medicine, Kyoto University, Japan.. amat@kuhp.kyoto-u.ac.jp) . Circulation, (1997 Sep 2) 96 (5) 1501-6. Journal code: 0147763. ISSN: 0009-7322. Pub. country: United States. Language: English.
AB BACKGROUND: Recent studies have shown that cytokines are capable of

modulating cardiovascular function and that some drugs used in the **treatment** of **heart failure** variably modulate the production of cytokines. To examine whether cardiac glycosides also modulate cytokine production, we evaluated the effects of ouabain on the production of cytokines in vitro and in vivo. METHODS AND RESULTS: Human peripheral blood mononuclear cells (PBMC) were obtained from healthy volunteers. PBMC were cultured with or without ouabain in the presence or absence of lipopolysaccharide (**LPS**). Ouabain induced the production of interleukin (IL)-1beta, IL-6, and tumor necrosis factor (TNF)-alpha in PBMC and induced mRNA of these cytokines, an induction apparently at the transcriptional level. Amiloride, staurosporin, and genistein inhibited cytokine production, and protein kinase C and tyrosine kinase appeared to be involved in the modulation of cytokine production induced by ouabain. However, when PBMC were stimulated with **LPS**, ouabain suppressed the production of IL-6 and TNF-alpha. To investigate whether ouabain modulates cytokine production in vivo, we evaluated the effects of ouabain in **LPS**-treated mice. Ouabain was found to protect against **LPS**-induced lethal toxicity in mice and decreased circulating IL-6 and TNF-alpha levels in vivo. CONCLUSIONS: These previously unrecognized immunomodulating effects of a cardiac glycoside may explain either the beneficial or the detrimental effects of these drugs in **heart failure** patients.

L13 ANSWER 41 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

97325610 EMBASE Document No.: 1997325610. Effect of L-lysine on nitric oxide overproduction in endotoxic shock. Liaudet L.; Gnaegi A.; Rosselet A.; Markert M.; Boulat O.; Perret C.; Feihl F.. F. Feihl, Institute of Pathophysiology, University Hospital-BH 19-313, CH-1011 Lausanne, Switzerland. British Journal of Pharmacology 122/4 (742-748) 1997. Refs: 43.
ISSN: 0007-1188. CODEN: BJPCBM. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB 1. An enhanced production of nitric oxide (NO) from L-arginine, related to the diffuse expression of an inducible NO synthase (iNOS), contributes to the pathogenesis of endotoxic shock. Since iNOS activity depends on extracellular L-arginine, we hypothesized that limiting cellular L-arginine uptake would reduce NO production in endotoxic shock. We investigated the effects of L-lysine, an inhibitor of L-arginine uptake through system y+, on NO production, multiple organ dysfunction and lactate levels, in normal and endotoxaemic rats. 2. Anaesthetized rats challenged with intravenous lipopolysaccharide (**LPS**, 10 mg kg-1) received a 5 h infusion of either L-lysine (500 μmol kg-1 h-1, n = 12) or isotonic saline (2 ml kg-1 h-1, n = 11). In rats treated with saline, **LPS** produced a large increase in plasma nitrate and L-citrulline concentrations at 5 h, both markers of enhanced NO production. **LPS** also caused severe hypotension, low cardiac output and marked hyperlactataemia. All these changes were significantly reduced by L-lysine administration. 3. Endotoxaemia also caused a significant rise in the plasma levels of alanine aminotransferase (ALAT), lipase, urea and creatinine, and hence, liver, pancreatic and renal dysfunction. These changes tended to be less pronounced in rats treated with L-lysine, although the differences did not reach statistical significance. 4. Similar experiments were conducted in 10 rats challenged with **LPS** vehicle in place of **LPS** and then treated with L-lysine (500 μmol kg-1 h-1, n = 5) or saline (2 ml kg-1 h-1, n = 5) for 5 hr. In these animals, all the haemodynamic and metabolic variables remained stable and not statistically different between both **treatment** groups, except for a slight rise in ALAT, which was comparable in L-lysine and saline-treated rats. 5. In conclusion, L-lysine, an inhibitor of cellular L-arginine uptake, reduces NO production and exerts beneficial haemodynamic effects in endotoxaemic rats. L-lysine also reduces hyperlactataemia and tends to blunt the development of organ injury in these animals. Contrastingly, L-lysine has no effects in the absence of endotoxin and thus appears to act as a selective modulator of iNOS

activity.

L13 ANSWER 42 OF 46 MEDLINE on STN DUPLICATE 11
97177413. PubMed ID: 9024938. Vesnarinone is a selective inhibitor of macrophage TNF(alpha) release. Kambayashi T; Mazurek N; Jacob C O; Wei N; Fong M; Strassmann G. (Department of Immunology, Otsuka-America Pharmaceutical Inc., Rockville, MD 20850, USA.) International journal of immunopharmacology, (1996 Jun-Jul) 18 (6-7) 371-8. Journal code: 7904799. ISSN: 0192-0561. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Vesnarinone is an experimental drug that has been used successfully in the **treatment** of congestive **heart failure** patients. In this report we investigate the effect of vesnarinone on the cytokine secretory products of mononuclear phagocytes. In a concentration-dependent manner, the drug inhibits the endotoxin(**LPS**)-stimulated release of tumor necrosis factor (TNF) alpha and suppresses interleukin(IL)-6 release, but does not affect the release of IL-1 alpha, IL-10 and leukemia inhibitory factor (LIF) by mouse peritoneal macrophages. Using competitive polymerase chain reaction (PCR) analyses, we find that vesnarinone significantly reduces TNF(alpha), but not IL-10 mRNA. In addition to **LPS**, the drug inhibits TNF(alpha) release induced by several other stimuli. The inhibitory effect of the drug on the TNF(alpha) biosynthesis can be observed in differentiated human monocytes, in macrophage cell lines, and in synovial adherent cells from rheumatoid arthritis patients. Although the precise mode of action of vesnarinone in the signal transduction pathway leading to the selective inhibition of TNF(alpha) is not known, the drug might be useful in the **treatment** of diseases involving that cytokine.

L13 ANSWER 43 OF 46 MEDLINE on STN DUPLICATE 12
96046812. PubMed ID: 7585804. Vesnarinone inhibits induction of nitric oxide synthase in J774 macrophages and rat cardiac myocytes in culture. Hattori Y; So S; Hattori S; Kasai K; Shimoda S. (Department of Endocrinology, Internal Medicine, Dokkyo University School of Medicine, Tochigi, Japan.) Cardiovascular research, (1995 Aug) 30 (2) 187-92. Journal code: 0077427. ISSN: 0008-6363. Pub. country: Netherlands. Language: English.

AB OBJECTIVE: We investigated whether vesnarinone alters the induction of nitric oxide (NO) synthesis by bacterial lipopolysaccharide (**LPS**) or in combination with interferon-gamma in cultured J774 macrophages and rat cardiac myocytes. METHODS: The induction of NO synthesis was determined by measuring the stable end-product nitrite. The cytotoxic effect of vesnarinone was assessed by measuring cell respiration. Any change in mRNA levels for NO synthase (NOS) was determined by RT-PCR. RESULTS: Stimulation by **LPS** or in combination with interferon-gamma increased the accumulation of nitrite in the supernatant of J774 macrophages or cardiac myocytes. NOS induction accounted for this accumulation of nitrite, as dexamethasone, NG-methyl-L-arginine, and cycloheximide each reduced the production of nitrite in both types of cells. Vesnarinone produced a significant decline in the cumulative production of nitrite in both types of cells without evidence of cytotoxicity. However, the addition of vesnarinone after induction of NOS did not inhibit nitrite production. **Treatment** with **LPS** or in combination with interferon-gamma led to a significant expression of NOS mRNA in both types of cells that was significantly reduced by vesnarinone. CONCLUSIONS: Vesnarinone inhibited NO synthesis by inhibiting the induction of NOS in J774 macrophages and cardiac myocytes. This drug may exert a beneficial effect in patients with **heart failure**, in part, by attenuating the production of NO.

L13 ANSWER 44 OF 46 MEDLINE on STN DUPLICATE 13
95057852. PubMed ID: 7968253. Vesnarinone prolongs survival and reduces lethality in a murine model of lethal endotoxemia. Matsui S; Matsumori A; Sasayama S. (Department of Internal Medicine, Kyoto University Hospital, Japan.) Life sciences, (1994) 55 (22) 1735-41. Journal code: 0375521. ISSN: 0024-3205. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Vesnarinone (3,4-Dihydro-6-[4(3,4-dimethoxybenzoyl)-1-piperanizyl]-2(1H)-quino linone), a recently synthesized quinolinone derivative with positive inotropic properties, has been reported the survival of patients with chronic congestive **heart failure.** However, the mechanisms that contribute to this improvement are not yet well understood. There is increasing evidence that vesnarinone has novel immunosuppressive properties related to its inhibition of cytokine production. Cytokines have been shown to play a pivotal role in the pathophysiologic consequences of fatal bacteremic shock. In this study, we investigated the effects of vesnarinone in a murine model of lethal endotoxemia induced by lipopolysaccharide (**LPS**). Eight-week-old female BALB/c mice were given 300 or 400 micrograms of **LPS**, and 50 or 100 mg/kg of vesnarinone was administered by oral gavage and/or 10 or 30 micrograms of vesnarinone was given intra peritoneally. Vesnarinone prolonged the median survival time and reduced lethality when given at the same time as the **LPS** injection. However, vesnarinone did not have a beneficial effect when administered 2 hours after **LPS treatment.** Plasma TNF-alpha reached a maximum level 1 hour after **LPS** challenge, and vesnarinone reduced the plasma level of TNF-alpha, when administered at the same time as **LPS** injection. Vesnarinone had protective effects against lethal endotoxemia; these effects were considered to be due to the suppression of TNF-alpha production. These findings suggest that vesnarinone may be a promising agent for the **treatment** of bacterial sepsis and shock.

L13 ANSWER 45 OF 46 MEDLINE on STN DUPLICATE 14

94170507. PubMed ID: 8124835. Vesnarinone, a new inotropic agent, inhibits cytokine production by stimulated human blood from patients with **heart failure.** Matsumori A; Shioi T; Yamada T; Matsui S; Sasayama S. (Department of Internal Medicine, Faculty of Medicine, Kyoto University, Japan.) Circulation, (1994 Mar) 89 (3) 955-8. Journal code: 0147763. ISSN: 0009-7322. Pub. country: United States. Language: English.

AB BACKGROUND: Vesnarinone, a quinolinone derivative, is a recently synthesized positive inotropic agent that has been shown to dramatically improve the survival of patients with **heart failure.** However, the mechanism of action of vesnarinone remains unknown. Reversible neutropenia complicated with vesnarinone therapy suggests that vesnarinone may modulate the production of cytokines. Because tumor necrosis factor (TNF)-alpha and other cytokines have been shown to depress myocardial contractility, we investigated the effects of vesnarinone on the production of various cytokines. METHODS AND RESULTS: We studied the effects of vesnarinone on cytokine production by lipopolysaccharide (**LPS**)-stimulated whole blood from seven patients with **heart failure** and from five healthy volunteers. Heparinized blood was diluted in RPMI and stimulated with **LPS.** Vesnarinone was added in a range of 1 to 30 micrograms/mL, the blood was incubated for 24 hours, and interleukin (IL)-1 alpha, IL-1 beta, IL-6, TNF-alpha, interferon (IFN)-gamma, and granulocyte colony-stimulating factor (G-CSF) were measured by an enzyme-linked immunosorbent assay. **LPS** stimulation induced a more prominent increase in TNF-alpha in patients with **heart failure** than in healthy volunteers. Vesnarinone inhibited the production of TNF-alpha and IFN-gamma both in healthy volunteers and in patients with **heart failure.** IL-1 alpha and IL-1 beta were also suppressed in healthy volunteers, but this response was variable, and a significant reduction was not seen in patients with **heart failure.** Marked inhibition of G-CSF and other cytokines by vesnarinone was observed in one patient who had developed neutropenia as a result of vesnarinone therapy. CONCLUSIONS: Although the number of study patients was small and the results are preliminary, these findings provide evidence that vesnarinone plays an important role in the regulation of cytokines and suggest that the reduction of cytokine release may contribute to the beneficial effects of the drug in the **treatment** of **heart failure** . Furthermore, the measurement of cytokines may be useful in predicting the occurrence of neutropenia, which has been occasionally reported in

patients treated with vesnarinone.

L13 ANSWER 46 OF 46 MEDLINE on STN DUPLICATE 15
94029956. PubMed ID: 8216257. Vesnarinone inhibits production of HIV-1 in cultured cells. Maruyama I; Maruyama Y; Nakajima T; Kitajima I; Osame M; Zhao J Q; Chen I S; Nakai S; Ikeda M; Yabu-uchi Y; +. (Department of Clinical Medicine, School of Medicine, Kagoshima University, Japan.) Biochemical and biophysical research communications, (1993 Sep 30) 195 (3) 1264-71. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.
AB Vesnarinone, a synthetic oral cardiotonic agent that has been used for **treatment** of patients with congestive **heart failure**, was found to inhibit replication of HIV-1 in a peripheral blood lymphocytes model and in chronically infected macrophages at clinically achieved concentrations. Vesnarinone has no direct inhibitory activity against the reverse transcriptase of HIV-1, syncytium formation in short term assays, or retroviral protease. In addition, vesnarinone inhibits production of TNF-alpha and IL-6 by human peripheral blood mononucleated cells stimulated with **LPS**. These observations suggest that vesnarinone may be therapeutically useful in patients infected with HIV-1.

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     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 16:18:06 ON
     15 JUN 2004
L1             1 S CHEODEOXYCHOLIC ACID
L2            33 S CHEMODEOXYCHOLIC ACID
L3            13 S L2 AND TREATMENT
L4            13 DUP REMOVE L3 (0 DUPLICATES REMOVED)
L5         22161 S CHOLIC ACID
L6             1 S L5 AND CHRONIC HEART FAILURE
L7         13576 S DEOXYCHOLIC ACID
L8          1991 S L7 AND TREATMENT
L9             0 S L8 AND CHRONIC HEART FAILURE
L10       138882 S LPS
L11          266 S L10 AND HEART FAILURE
L12           89 S L11 AND TREATMENT
L13           46 DUP REMOVE L12 (43 DUPLICATES REMOVED)

=> s l13 and chronic
L14           11 L13 AND CHRONIC

=> dup remove l14
PROCESSING COMPLETED FOR L14
L15           11 DUP REMOVE L14 (0 DUPLICATES REMOVED)

=> d l15 1-11 cbib abs

L15  ANSWER 1 OF 11      MEDLINE on STN
2004283437.    PubMed ID: 15182775.   Selective intestinal decontamination in advanced chronic heart failure: a pilot trial. Conraads Viviane M; Jorens Philippe G; De Clerck Luc S; Van Saene Hendrik K; Ieven Margaretha M; Bosmans Johan M; Schuerwegh Annemie; Bridts Chris H; Wuyts Floris; Stevens Wim J; Anker Stefan D; Rauchhaus Mathias; Vrints Christiaan J. (Department of Cardiology, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium. ) European journal of heart failure : journal of the Working Group on Heart Failure of the European Society of Cardiology, (2004 Jun) 6 (4) 483-91. Journal code: 100887595. ISSN: 1388-9842. Pub. country: Netherlands. Language: English.
AB   Background and aims: Endotoxin, derived from intestinal aerobic Gram-negative bacilli (AGNB), could be an important monocyte activator in
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chronic heart failure (CHF). The effect of selective decontamination of the digestive tract (SDD) on intracellular monocyte cytokine production, monocyte CD14 expression, circulating endotoxin and cytokines, and flow-mediated dilation (FMD) was studied in patients with severe CHF. Methods and results: Ten patients with CHF (NYHA class III-IV) were enrolled in a non-placebo controlled pilot trial involving the administration of SDD (polymyxin B, tobramycin) for 8 weeks. One patient was later excluded due to cardiac transplantation. Before **treatment**, after 4 and 8 weeks therapy, and 6 weeks post-**treatment**, monocyte CD14 expression, intracellular monocyte production of interleukin-1beta [IL-1beta], interleukin-6 [IL-6], tumour necrosis factor (TNF)-alpha with and without lipopolysaccharide (**LPS**) stimulation were measured. Concentrations of endotoxin and cytokines (IL-1beta, IL-6, TNF-alpha) were also determined. AGNB in faeces, intestinal endotoxin and FMD were assessed at baseline, after 4 weeks of **treatment** and 6 weeks post-**treatment.** SDD eradicated intestinal AGNB (P<0.00001) and decreased faecal endotoxin concentrations (P<0.00001). There was a significant decline in monocyte CD14 expression (P=0.03) and in IL-1beta (P=0.0001), IL-6 (P=0.02) and TNF-alpha (P=0.0002) production after 4 and 8 weeks of **treatment** in the basal state and for IL-1beta (P=0.008) and IL-6 (P=0.005) after **LPS** stimulation. FMD significantly improved at 4 weeks and returned to baseline after **treatment** discontinuation (P=0.002). Circulating concentrations of endotoxin and cytokines remained unchanged. Conclusion: Reduction of the intestinal endotoxin pool led to a decrease in monocyte CD14 expression and intracellular cytokine production in patients with severe CHF. The improvement of peripheral endothelial function could be a marker of the anti-inflammatory effect of SDD.

L15 ANSWER 2 OF 11 EMBASE
on STN

2003363662 EMBASE Acceptable short-term results after endovascular repair of diseases of the thoracic aorta in high risk patients. Krohg-Sorensen K.; Hafsahl G.; Fosse E.; Geiran O.R.. K. Krohg-Sorensen, Dept. of Thorac./Cardiovasc. Surgery, Rikshositalet University Hospital, N-0027 Oslo, Norway. kirsten.krohg-sorensen@rikshospitalet.no. European Journal of Cardio-thoracic Surgery 24/3 (379-387) 1 Sep 2003.
Refs: 15.
ISSN: 1010-7940. CODEN: EJCSE7. Pub. Country: Netherlands. Language: English. Summary Language: English.

AB Objective: To report our experience with endovascular stentgraft repair of diseases of the descending thoracic aorta in high risk patients. Methods: Twenty-one procedures were performed in 20 patients (10 women), aged 22-81 years, for disease of the descending thoracic aorta with the Gore Excluder thoracic endoprosthesis® (WL Gore) (n=11) and the Talent **LPS** Stent Graft System (Medtronic AVE) (n=10). All patients were considered high operative risk. Diagnoses included saccular aneurysm, aneurysm rupture, mycotic aneurysm, penetrating atherosclerotic ulcer, aortic dissection and aortitis. The access vessels were a tube graft of the (thoraco-) abdominal aorta (n=4), the common iliac (n=6) and the common femoral artery (n=11). Several patients needed major cardiovascular surgery for concomitant disease during the same stay. Computed tomography scan and chest X-ray was performed at 3 and 6 months and thereafter every sixth month postoperatively. Results: Two patients died. One had a colon perforation 8 days postoperatively and died after 3.5 months, and the other with preoperative sepsis and a mycotic aneurysm died on day 11 from cardiac and renal failure. In one patient the stentgraft dislocated during release, and an additional stentgraft had to be implanted 1 week later to treat the proximal leak. In another patient the stentgraft could not be released from the introducer, and was pulled back to the aortic bifurcation and retrieved through laparotomy. Eighteen patients have been followed for 1-24 months, and no migration, wire fractures or endoleak have been seen. There were no neurologic complications. One patient treated for infected pseudoaneurysm had a **chronic** graft infection. Conclusion: In this small number of patients with high

operative risk, short-term results of endovascular stentgraft repair of variable diseases of the descending aorta have been satisfactory. Stentgraft repair could be a valuable supplement to surgery for patients with complex multilevel or multiorgan disease. .COPYRGT. 2003 Elsevier B.V. All rights reserved.

L15 ANSWER 3 OF 11 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:576101 The Genuine Article (R) Number: 697RP. Myocardial IL-6 regulation by neurohormones - an in vitro superfusion study. Jeron A (Reprint); Kaiser T; Straub R H; Weil J; Riegger G A J; Muders F. Klinikum Univ Regensburg, Klin & Poliklin Innere Med 2, Franz Josef Strauss Allee 11, D-93042 Regensburg, Germany (Reprint); Klinikum Univ Regensburg, Klin & Poliklin Innere Med 2, D-93042 Regensburg, Germany; Klinikum Univ Regensburg, Klin & Poliklin Innere Med 1, D-93042 Regensburg, Germany. BRAIN BEHAVIOR AND IMMUNITY (AUG 2003) Vol. 17, No. 4, pp. 245-250. Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA. ISSN: 0889-1591. Pub. country: Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Interleukin-6 (IL-6) is expressed in the myocardium and has been implicated in cell proliferation, negative inotropic effects and myocardial hypertrophy. To determine whether myocardial IL-6 is modified by neuro-humoral and immunoregulatory stimuli, we studied the effects of lipopolysaccharide (**LPS**), corticosterone (CS), isoproterenol and angiotensin II on myocardial IL-6 secretion in superfused myocardium.

Methods: Slices of rat left ventricular myocardium were superfused in 80 mul chambers for up to 5 h. **LPS** (1, 50, and 100 mug/ml), CS (10(-7), 10(-6), and 10(-5) M, DSMO as vehicle), isoproterenol (10(-6), 10(-7), and 10(-8) M) and angiotensin II (10(-5), 10(-7), and 10(-9) M) were added to the culture medium at hour 2. IL-6 was measured in the perfusate by ELISA.

Results: Physiological corticosterone concentrations (10(-7) M) resulted in an increase in IL-6 concentration (142%) while high doses of steroid decreased IL-6 significantly (CS 10(-6) M: 88 +/- 14%, p <.05; CS 10(-5): 91 +/- 9%, p < .05) after 5 h. Left ventricular IL-6 secretion was significantly stimulated by **LPS** 50 mug/ml (3262 1684% vs. CTRL: 116 +/- 134%, p < .01). Isoproterenol **treatment** increased in IL-6 secretion compared to controls with and without CS, while angiotensin II reduced IL-6 concentration only in combination with CS.

Conclusion: Myocardial IL-6 secretion is modulated by physiological concentrations of corticosterone or angiotensin II and can be induced by **LPS** or isoproterenol, indicating a tight regulation of this cytokine. Suppression of cytokine expression within the heart might be a potential therapeutic goal in the **treatment** of various cardiovascular diseases. (C) 2003 Elsevier Science (USA). All rights reserved.

L15 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2002:888734 Document No. 137:384849 Preparation of 4-(4-pyridazinyl)pyrazole derivatives as p38MAP kinase (p38 mitogen-activated protein kinase) inhibitors. Minami, Nobuyoshi; Hasumi, Koichi; Ohta, Shuji; Sato, Shuichiro; Saito, Takahisa; Doi, Satoshi; Kobayashi, Motohiro; Sato, Jun; Asano, Hajime; Matsumoto, Yasuhiro (Teikoku Hormone Mfg. Co., Ltd., Japan). PCT Int. Appl. WO 2002092593 A1 20021121, 66 pp. DESIGNATED STATES: W: AU, CA, CN, JP, KR, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP4636 20020514. PRIORITY: JP 2001-146270 20010516.

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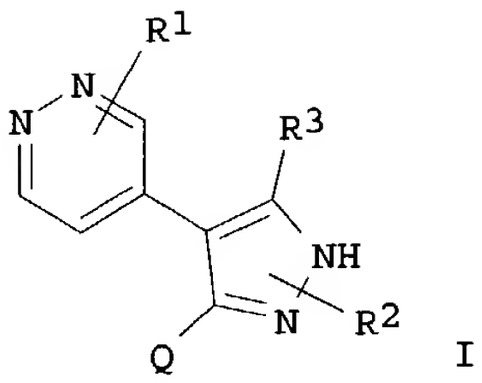

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AB 4-(4-Pyridazinyl)pyrazole derivs. represented by the following general formula (I) or salts thereof [wherein Q = optionally substituted aryl or heteroaryl; R1 = H, halogeno, HO, lower alkoxy, NH2, aralkylamino, mono- or di(lower alkyl)amino, lower alkylthio; R2 = H, lower alkynyl, optionally hydroxy-substituted lower alkyl; R3 = H, lower alkyl, CH2CH(R4)-(A)n-Y, CH:C(R4)-(A)n-Y, CH2CH(R4)-(A)n-Y, NR4-CO-(A)n-Y, lower cycloalkyl (wherein A = lower alkylene; Y = (un)substituted aryl; R4 = H, lower alkyl; n = 0, 1)] are prepared These compds. have an excellent inhibitory activity on p38 mitogen-activated protein kinase (p38MAPK), which is known to activate certain transcription factors such as TNF-κB, AP-1, and CREB binding to a DNA sequence common to tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and cyclooxygenase II (COX-II) and thus promoting the transcription and production of proteins such as TNF-α, IL-1, IL-6, and COX-II from mRNA. Thereby they inhibit the production of TNF-α, IL-1, IL-6, and COX-II and are useful for preventing or treating diseases associated with TNF-α, IL-1, IL-6, and COX-II. The above diseases include **chronic** articular rheumatism, multiple sclerosis, osteoarthritis (arthrosis deformans), psoriasis, HIV, asthma, septic shock, inflammatory bowel diseases, Crohn's disease, Alzheimer's disease, diabetes, cachexia, osteoporosis, graft-vs.-host disease, adult respiratory distress syndrome, arteriosclerosis, gout, glomerulonephritis, congestive **heart failure**, ulcerative colitis, septicemia, cerebral malaria, restenosis, hepatitis, systemic lupus erythematosus, thrombosis, born resorption disease, **chronic** pulmonary inflammation disease, heart reperfusion disorder, kidney reperfusion disorder, cancer, writer's syndrome, imminent abortion, eczema, allograft rejection, or seizure. They also include fever, Behcet's disease, neuralgia, meningitis, sunburn, contact dermatitis, acute synovitis, spondylitis, muscle degeneration, neovascularization, conjunctivitis, psoriatic arthritis, viral myocarditis, pancreatitis, hemorrhage, arthritis, endotoxin shock, parasitic infection, tuberculosis, myocardial infarction, Hansen's disease, diabetic retinopathy, irritable bowel syndrome (IBS), transplant rejection, burn, bronchitis, ischemic heart disease, eclampsia, pneumonia, remission of swelling, backache (low back pain), pharyngolaryngitis (pharyngitis-laryngitis), Kawasaki disease (mucocutaneous lymphnode syndrome), spinal cord disease, or atopic dermatitis. Thus, 2.0 M LiN(CHMe2)2/heptane-THF-ethylbenzene was added dropwise to a solution of 3.83 g 4-methylpyridazine in 40 mL THF at -70° and stirred at room temperature, followed by adding a solution of 6.84 g Et 4-fluorobenzoate in 40 mL THF at -70°, and the resulting mixture was stirred at room temperature for 3 h to give 40% 1-fluoro-4-(4-pyridazinylacetyl)benzene (II). To a solution of 4 g II in 80 mL THF was added 4.41 g N,N-dimethylformamide di-Me acetal and stirred at room temperature for 20 h, followed by distilling off the solvent under reduced pressure, and the residue was dissolved in 60 mL ethanol, treated with 1.85 g hydrazine monohydrate, and stirred at 50° for 30 min to give 79% 3(5)-(4-fluorophenyl)-4-(4-pyridazinyl)pyrazole (III). In a p38MAP kinase-binding inhibitory assay, III in vitro showed IC50 of 6.5 nM for inhibiting the binding of a radioligand, [3H]-SB202190, i.e. 4-(4-fluorophenyl)-2-(4-hydroxy-3,4-di-3H-phenyl)-5-(4-pyridyl)imidazole, on cytosol of human monocyte THP-1 cell. III at 30 mg/kg in vivo

inhibited the lipopolysaccharide (**LPS**)-induced production of TNF-α in mice by 84% after 6 h.

L15 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2002:315096 Document No. 136:320419 Human IL-17-related protein LP-48 and therapeutic use thereof. Glasebrook, Andrew Lawrence; Liu, Ling; Newton, Christy Michelle; Tetreault, Jonathan Wendell (Eli Lilly and Company, USA). PCT Int. Appl. WO 2002033083 A2 20020425, 112 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US27737 20010928. PRIORITY: US 2000-PV240177 20001013; US 2001-PV309936 20010803.

AB The invention provides protein and cDNA sequences for a novel human IL-17-related protein called LP-48 (also known as IL-17C and IL-21), which is a member of interleukin superfamily. The transgenic mice expressing LP-48 are used to test the function of LP-48 and possible therapeutic applications. LP-48 can protect the transgenic mice against **LPS**-induced septic shock and from **LPS**-induced death. LP-48 protein can inhibit **LPS**-induced increases in IFN-γ, IL-12, TNF-α and IL-6 secretion in transgenic mice. LP-48 can reduce apoptosis in human endothelial cells, more specifically, apoptosis induced by staurosporine. LP-48 can bind to the cell surface of endothelial cells and other tissues specifically through natural LP-48 receptors. Methods are provided for the **treatment** or prevention of atherosclerosis, allergic autoimmune diseases, endothelial cell apoptosis, allograft vasculopathy, hypertension, congestive **heart failure**, ischemia/reperfusion injury, type 1 diabetes, inflammation, immunodeficiencies, cancers, and infectious diseases by administering a human IL-17 related polypeptide and/or an antibody recognizing an epitope thereof to a patient in need of such therapy.

L15 ANSWER 6 OF 11 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2002294975 EMBASE Effect of interleukin-10 on the production of tumor necrosis factor-alpha by peripheral blood mononuclear cells from patients with **chronic heart failure.** Bolger A.P.; Sharma R.; Von Haehling S.; Doehner W.; Oliver B.; Rauchhaus M.; Coats A.J.S.; Adcock I.M.; Anker S.D.. A.P. Bolger, Department of Clinical Cardiology, National Heart and Lung Institute, London SW3 6LY, United Kingdom. a.bolger@ic.ac.uk. American Journal of Cardiology 90/4 (384-389) 15 Aug 2002.
Refs: 29.
ISSN: 0002-9149. CODEN: AJCDAG.
Publisher Ident.: S 0002-9149(02)02494-3. Pub. Country: United States.
Language: English. Summary Language: English.

AB **Chronic heart failure** (HF) is a state of inflammatory immune activation characterized by elevated circulating levels of tumor necrosis factor-α (TNF-α). Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine that inhibits TNF-α production and lessens endotoxin bioactivity. It is not known whether IL-10 reduces lipopolysaccharide (**LPS**) stimulated TNF-α production of peripheral blood mononuclear cells (PBMCs) from patients with **chronic** HF. PBMCs were isolated from 15 patients with **chronic** HF (New York Heart Association functional class 3.0 ± 0.2, left ventricular ejection fraction 30 ± 2%, peak oxygen consumption 18.1 ± 0.8 ml/kg/min) and 15 healthy control subjects and stimulated with 1 and 10 ng/ml **LPS** for 24 hours with or without prior addition of IL-10 (10 ng/ml). TNF-α was quantified in cell-free supernatants by an enzyme-linked immunosorbent assay.

TNF-α, soluble TNF receptors, IL-10, and **LPS** were quantified in plasma. **LPS** stimulated TNF-α production was highest in those patients in New York Heart Association class II ($p < 0.01$ vs New York Heart Association class III and IV, $p < 0.001$ vs control subjects). IL-10 reduced PBMC TNF-α production in all stimulated samples at 1 and 10 ng/ml **LPS** (mean reduction 43% at 1 ng/ml, $p < 0.01$ and 55% at 10 ng/ml, $p < 0.0001$). The percentage reduction in TNF-α release did not differ significantly between patients and control subjects or with respect to severity of **chronic** HF or baseline immune parameters. Independently of clinical severity, IL-10 profoundly inhibits TNF-α release from PBMCs isolated from patients with **chronic** HF. IL-10 is, therefore, a potential therapy for use in **chronic** HF associated with inflammatory immune activation. .COPYRGT.'2002 by Excerpta Medica, Inc.

L15 ANSWER 7 OF 11 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:242294 The Genuine Article (R) Number: 409BT. Ace-inhibition with quinapril modulates the nitric oxide pathway in normotensive rats.
Bachetti T; Comini L; Pasini E; Cargnoni A; Curello S; Ferrari R (Reprint) . Univ Ferrara, Osped S Anna, Nuove Clin, Corso Giovecca 203, I-44100 Ferrara, Italy (Reprint); Univ Ferrara, Chair Cardiol, I-44100 Ferrara, Italy; Spedali Civili, Div Cardiol, I-25125 Brescia, Italy; IRCCS, Cardiovasc Pathophysiol Res Ctr, Salvatore Maugeri Fdn, Gussago, Italy.
JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY (MAR 2001) Vol. 33, No. 3, pp. 395-403. Publisher: ACADEMIC PRESS LTD. 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND. ISSN: 0022-2828. Pub. country: Italy. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Angiotensin-converting enzyme (ACE) inhibitors exert some cardiovascular benefits by improving endothelial function. We evaluated the effects of **chronic treatment** with quinapril (Q) on the (L)-arginine/nitric oxide (NO) pathway in normotensive rats under baseline and inflammatory conditions. The role of bradykinin was also investigated. The animals received for 1 week either the ACE-inhibitor Q (1 and 10 mg/kg/day). the B-2, receptor antagonist HOE 140, Q + HOE 140, or no drug. At the end of **chronic treatment**, rats underwent either a 6-h placebo or an E. coli endotoxin challenge. The following measurements were made: (i) endothelial and inducible NO synthase (eNOS and iNOS) protein expression: (ii) eNOS/iNOS activity; (iii) serum levels of nitrite/ nitrate and tumour necrosis factor (TNF)-alpha; (iv) NO in the expired air (eNO). Q increased baseline aortic eNOS protein expression (up to 99%, $P<0.001$) and activity ((L)-citrulline synthesis up to 94%. $P<0.01$; serum nitrite/ nitrate up to 55%, $P<0.05$). HOE 140 partially reversed Q-induced upregulation of eNOS ($P<0.05$). Moreover, Q counteracted **LPS** effects, i.e. increased the impaired eNOS pathway and limited iNOS induction (up to 94 and 24%, respectively), and reduced the increased nitrite/nitrate and TNF-alpha serum levels as well as eNO (up to 25, 38 and 28%, respectively. $P<0.01$ for all comparisons). HOE 140 did not influence Q effects on iNOS during endotoxaemia. In conclusion, in (patho)physiological conditions in rats, Q up-regulated eNOS with a bradykinin-mediated mechanism. while downregulated iNOS with a possible TNF-<alpha>-mediated mechanism. (C) 2001 Academic Press.

L15 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2000:608753 Document No. 133:193275 Preparation of phosphoric acid derivatives as TNF-α production inhibitors. Matsui, Toshiaki; Ohmawari, Nagashige (Ono Pharmaceutical Co., Ltd., Japan). PCT Int. Appl. WO 2000050429 A1 20000831, 253 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION:

WO 2000-JP1005 20000222. PRIORITY: JP 1999-44840 19990223; JP 1999-283104 19991004.

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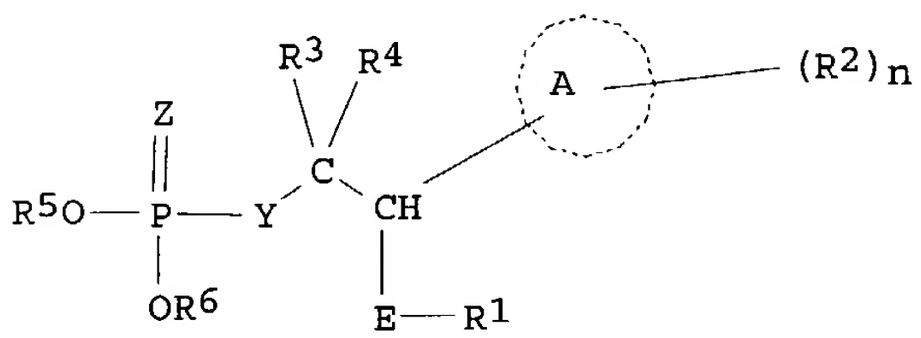

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AB The title compds. I [R1 = alkyl, etc.; ring A = heterocyclic ring, etc.; R2 = NR7CO, etc.; R7 = H, alkyl; R3, R4 = H, alkyl, etc.; further details on R3 and R4 are given; n = 0 or n ≥ 1; R5, R6 = H, alkyl, Ph, etc.; E = NR7CO, etc.; Y, Z = O, S; provisos are given] are prepared I are useful as preventives and/or remedies for rheumatoid arthritis, ulcerative colitis, Crohn's disease, hepatitis, sepsis, hemorrhagic shock, multiple sclerosis, brain infarction, diabetes, interstitial pneumonia, uveitis, pain, glomerulonephritis, HIV-associated diseases, cachexia, myocardial infarction, **chronic heart failure**, Hansen's disease, infection, etc. (2R)-2-Phenyl-2-(N-octanoylamino)ethyl phosphate disodium salt showed ED50 of 2.6 mg/kg against TNF-α production in mice treated with **LPS**. A formulation is given.

L15 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2000:513526 Document No. 133:134187 Method of treating **chronic** cardiac disease. Giroir, Brett P.; Scannon, Patrick J. (Xoma Technology Ltd., USA; Board of Regents, the University of Texas System). PCT Int. Appl. WO 2000043028 A2 20000727, 36 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US1515 20000121. PRIORITY: US 1999-PV116736 19990122.

AB New therapeutic uses for bactericidal/permeability-increasing (BPI) protein products that involve **treatment** of **chronic** cardiac disease. The **chronic** cardiac diseases include **chronic** congestive **heart failure**, cardiomyopathy, and congenital heart defect. The patients with **chronic** cardiac disease exhibit elevated level of circulating **LPS** and LBP.

L15 ANSWER 10 OF 11 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:437776 The Genuine Article (R) Number: 202TG. Endotoxin and immune activation in **chronic heart failure**: a prospective cohort study. Niebauer J; Volk H D; Kemp M; Dominguez M; Schumann R R; Rauchhaus M; PooleWilson P A; Coats A J S; Anker S D (Reprint). NATL HEART & LUNG INST, IMPERIAL COLL SCH MED, DOVEHOUSE ST, LONDON SW3 6LY, ENGLAND (Reprint); NATL HEART & LUNG INST, IMPERIAL COLL SCH MED, LONDON SW3 6LY, ENGLAND; UNIV LEIPZIG, HERZZENTRUM, LEIPZIG, GERMANY; UNIV KLINIKUM CHARITE, INST MED IMMUNOL, BERLIN, GERMANY; HAREFIELD HOSP, HEART SCI CTR, HAREFIELD, MIDDX, ENGLAND; UNIV KLINIKUM CHARITE, INST MIKROBIOL & HYG, BERLIN, GERMANY; MAX DELBRUCK CTR MOL MED, FRANZ VOLHARD KLIN, BERLIN, GERMANY. LANCET (29 MAY 1999) Vol. 353, No. 9167, pp. 1838-1842. Publisher: LANCET LTD. 42 BEDFORD SQUARE, LONDON WC1B 3SL, ENGLAND. ISSN: 0140-6736. Pub. country: ENGLAND; GERMANY. Language:

English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background. Immune activation in patients with **chronic heart failure** may be secondary to endotoxin (lipopolysaccharide) action. We investigated the hypothesis that altered gut permeability with bacterial translocation and endotoxaemia would be increased in patients with oedema secondary to congestive **heart failure.**

Methods. We compared 20 patients who had **chronic heart failure** with recent-onset peripheral oedema (mean age 64 years [SD 10], New York Heart Association [NYHA] class 3.3 [0.7]), 20 stable non-oedematous patients with **chronic heart failure** (mean age 63 years [19], NYHA class 2.6 [0.7]), and 14 healthy volunteers (mean age 55 years [16]). Biochemical markers of endotoxaemia, inflammation, and immune activation were measured. Ten patients were studied within 1 week of complete resolution of oedema. Five patients survived longer than 6 months and were restudied again after remaining free of oedema for more than 3 months.

Findings. Mean endotoxin concentrations were higher in oedematous patients with **chronic heart failure** than in stable patients with **chronic heart failure** (0.74 [SD 0.45] vs 0.37 EU/mL [0.23], p = 0.0009) and controls (0.46 EU/mL [0.21], p = 0.02). Oedematous patients had the highest concentrations of several cytokines. After short-term diuretic **treatment**, endotoxin concentrations decreased from 0.84 EU/mL [0.49] to 0.45 EU/mL [0.21], p < 0.05) but cytokines remained raised. After freedom of oedema for more than 3 months after oedema resolved, endotoxin concentrations remained unchanged from the previous visit (0.49 EU/mL [0.06], p = 0.45).

Interpretation. Raised concentrations of endotoxin and cytokines are found in patients with **chronic heart failure** during acute oedematous exacerbation. Intensified diuretic **treatment** can normalise endotoxin concentrations. Our preliminary findings suggest that endotoxin may trigger immune activation in patients with **chronic heart failure** during oedematous episodes.

L15 ANSWER 11 OF 11 MEDLINE on STN

95057852. PubMed ID: 7968253. Vesnarinone prolongs survival and reduces lethality in a murine model of lethal endotoxemia. Matsui S; Matsumori A; Sasayama S. (Department of Internal Medicine, Kyoto University Hospital, Japan.) Life sciences, (1994) 55 (22) 1735-41. Journal code: 0375521. ISSN: 0024-3205. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Vesnarinone (3,4-Dihydro-6-[4(3,4-dimethoxybenzoyl)-1-piperanizyl]-2(1H)-quino linone), a recently synthesized quinolinone derivative with positive inotropic properties, has been reported the survival of patients with **chronic** congestive **heart failure.** However, the mechanisms that contribute to this improvement are not yet well understood. There is increasing evidence that vesnarinone has novel immunosuppressive properties related to its inhibition of cytokine production. Cytokines have been shown to play a pivotal role in the pathophysiologic consequences of fatal bacteremic shock. In this study, we investigated the effects of vesnarinone in a murine model of lethal endotoxemia induced by lipopolysaccharide (**LPS**). Eight-week-old female BALB/c mice were given 300 or 400 micrograms of **LPS**, and 50 or 100 mg/kg of vesnarinone was administered by oral gavage and/or 10 or 30 micrograms of vesnarinone was given intra peritoneally. Vesnarinone prolonged the median survival time and reduced lethality when given at the same time as the **LPS** injection. However, vesnarinone did not have a beneficial effect when administered 2 hours after **LPS treatment.** Plasma TNF-alpha reached a maximum level 1 hour after **LPS** challenge, and vesnarinone reduced the plasma level of TNF-alpha, when administered at the same time as **LPS** injection. Vesnarinone had protective effects against lethal endotoxemia; these effects were considered to be due to the suppression of TNF-alpha production. These findings suggest that vesnarinone may be a promising

agent for the **treatment** of bacterial sepsis and shock.

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L16             0 L13 AND ACUTE FAILURE

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L17            11 L13 AND ACUTE

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L18  ANSWER 1 OF 11  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
2004051205  EMBASE  Altered expression of nuclear hormone receptors and
     coactivators in mouse heart during the acute-phase response.
     Feingold K.; Kim M.S.; Shigenaga J.; Moser A.; Grunfeld C.. K. Feingold,
     Metabolism Section (111F), Dept. of Vet. Affairs Medical Center, 4150
     Clement St., San Francisco, CA 94121, United States. kfngld@itsa.ucsf.edu.
     American Journal of Physiology - Endocrinology and Metabolism  286/2 49-2
     (E201-E207)  2004.
     Refs: 66.
     ISSN: 0193-1849. CODEN: AJPMD. Pub. Country: United States. Language:
     English. Summary Language: English.
AB   Severe sepsis results in the decreased uptake and oxidation of fatty acids
     in the heart and cardiac failure. Some of the key proteins required for
     fatty acid uptake and oxidation in the heart have been shown to be
     downregulated after endotoxin (LPS) administration. The nuclear
     hormone receptors, peroxisome proliferator-activated receptor (PPAR) and
     thyroid receptor (TR), which heterodimerize with the retinoid X receptor
     (RXR), are important regulators of fatty acid metabolism and decrease in
     the liver after LPS administration. In the present study, we
     demonstrate that LPS treatment produces a rapid and
     marked decrease in the mRNA levels of all three RXR isoforms, PPARα
     and PPARδ, and TRα and TRβ in the heart. Moreover,
     LPS administration also decreased the expression of the
     coactivators CREB-binding protein (CBP)/p300, steroid receptor coactivator
     (SRC)-1, SRC-3, TR-associated protein (TRAP)220, and PPARγ
     coactivator (PGC)-1, all of which are required for the transcriptional
     activity of RXR-PPAR and RXR-TR. In addition, the mRNA levels of the
     target genes malic enzyme, Spot 14, sarcoplasmic reticulum Ca(2+)-ATPase,
     or SERCA2, the VLDL receptor, fatty acyl-CoA synthetase, fatty acid
     transporter/CD36, carnitine palmitoyltransferase Iβ, and lipoprotein
     lipase decrease in the heart after LPS treatment. The
     decrease in expression of RXRα, -β, and -γ, PPARα
     and -δ, and TRα and -β, and of the coactivators CBP/p300,
     SRC-1, SRC-3, TRAP220, and PGC-1 and the genes they regulate, induced by
     LPS in the heart, could account for the decreased expression of
     key proteins required for fatty acid oxidation and thereby play an
     important role in cardiac contractility. These alterations could
     contribute to the myocardial dysfunction that occurs during sepsis.

L18  ANSWER 2 OF 11  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
2003403291  EMBASE  Urgent thoracic aortal dissection and aneurysm:
     Treatment with stent-graft implantation in an angiographic suite.
     Balzer J.O.; Doss M.; Thalhammer A.; Fieguth H.-G.; Moritz A.; Vogl T.J..
     J.O. Balzer, Dept. of Diagn./Intervent. Radiology, University Clinic
     Frankfurt/Main, Johann Wolfgang Goethe University, Theodor-Stern-Kai 7,
     60590 Frankfurt, Main, Germany. j.o.balzer@em.uni-frankfurt.de. European
     Radiology  13/10 (2249-2258)  1 Oct 2003.
     Refs: 22.
```

ISSN: 0938-7994. CODEN: EURAE3. Pub. Country: Germany. Language: English. Summary Language: English.

AB The aim of this study was to evaluate the feasibility of endoluminal stent-graft placement in an angiographic suite for the **treatment** of emergent type-B aortic dissections and ruptured thoracic aortal aneurysms. Twenty-six patients with either urgent type-B dissection (n=8) or aneurysms (n=18) of the descending thoracic aorta were chosen for stent-graft implantation. All patients received a multidetector-row CT angiography of the whole aorta and pelvic arteries prior to stent-graft implantation. All procedures were performed in a fully equipped digital subtraction angiography (DSA) suite under general anesthesia. In 20 patients Talent **LPS** tube grafts and in 4 patients an Excluder graft were used. Access was achieved via surgical cut-down in the left (n=7) or right (n=19) groin. Sealing was successful in 24 patients. The proximal covered portion of the stent graft was placed across the left subclavian artery in 2 patients. Procedural success was achieved in 23 of 24 patients. One patient required a second stent-graft placement before the aneurysm was sealed. One patient with an **acute** perforation of the descending aorta died due to cardiac failure prior to stent-graft implantation. In 1 patient stent-graft delivery failed due to severe calcification of both common iliac arteries. Endoluminal **treatment** of both urgent type-B aortic dissections and thoracic aortal aneurysms with stent graft is an attractive alternative **treatment** to surgical repair. The placement of stent grafts in an angiographic suite is a safe and feasible method with good clinical effectiveness and, so far, good clinical outcome.

L18 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN

2002:888734 Document No. 137:384849 Preparation of 4-(4-pyridazinyl)pyrazole derivatives as p38MAP kinase (p38 mitogen-activated protein kinase) inhibitors. Minami, Nobuyoshi; Hasumi, Koichi; Ohta, Shuji; Sato, Shuichiro; Saito, Takahisa; Doi, Satoshi; Kobayashi, Motohiro; Sato, Jun; Asano, Hajime; Matsumoto, Yasuhiro (Teikoku Hormone Mfg. Co., Ltd., Japan). PCT Int. Appl. WO 2002092593 A1 20021121, 66 pp. DESIGNATED STATES: W: AU, CA, CN, JP, KR, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP4636 20020514. PRIORITY: JP 2001-146270 20010516.

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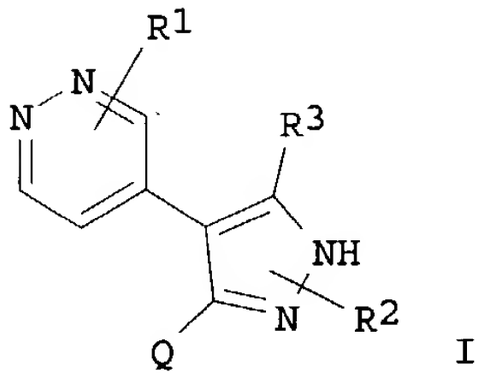

I

AB 4-(4-Pyridazinyl)pyrazole derivs. represented by the following general formula (I) or salts thereof [wherein Q = optionally substituted aryl or heteroaryl; R1 = H, halogeno, HO, lower alkoxy, NH2, aralkylamino, mono- or di(lower alkyl)amino, lower alkylthio; R2 = H, lower alkynyl, optionally hydroxy-substituted lower alkyl; R3 = H, lower alkyl, CH2CH(R4)-(A)n-Y, CH:C(R4)-(A)n-Y, CH2CH(R4)-(A)n-Y, NR4-CO-(A)n-Y, lower cycloalkyl (wherein A = lower alkylene; Y = (un)substituted aryl; R4 = H, lower alkyl; n = 0, 1)] are prepared These compds. have an excellent inhibitory activity on p38 mitogen-activated protein kinase (p38MAPK), which is known to activate certain transcription factors such as TNF-κB, AP-1, and CREB binding to a DNA sequence common to tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and cyclooxygenase II (COX-II) and thus promoting the

transcription and production of proteins such as TNF-α, IL-1, IL-6, and COX-II from mRNA. Thereby they inhibit the production of TNF-α, IL-1, IL-6, and COX-II and are useful for preventing or treating diseases associated with TNF-α, IL-1, IL-6, and COX-II. The above diseases include chronic articular rheumatism, multiple sclerosis, osteoarthritis (arthrosis deformans), psoriasis, HIV, asthma, septic shock, inflammatory bowel diseases, Crohn's disease, Alzheimer's disease, diabetes, cachexia, osteoporosis, graft-vs.-host disease, adult respiratory distress syndrome, arteriosclerosis, gout, glomerulonephritis, congestive **heart failure**, ulcerative colitis, septicemia, cerebral malaria, restenosis, hepatitis, systemic lupus erythematosus, thrombosis, born resorption disease, chronic pulmonary inflammation disease, heart reperfusion disorder, kidney reperfusion disorder, cancer, writer's syndrome, imminent abortion, eczema, allograft rejection, or seizure. They also include fever, Behcet's disease, neuralgia, meningitis, sunburn, contact dermatitis, **acute** synovitis, spondylitis, muscle degeneration, neovascularization, conjunctivitis, psoriatic arthritis, viral myocarditis, pancreatitis, hemorrhage, arthritis, endotoxin shock, parasitic infection, tuberculosis, myocardial infarction, Hansen's disease, diabetic retinopathy, irritable bowel syndrome (IBS), transplant rejection, burn, bronchitis, ischemic heart disease, eclampsia, pneumonia, remission of swelling, backache (low back pain), pharyngolaryngitis (pharyngitis-laryngitis), Kawasaki disease (mucocutaneous lymphnode syndrome), spinal cord disease, or atopic dermatitis. Thus, 2.0 M LiN(CHMe2)2/heptane-THF-ethylbenzene was added dropwise to a solution of 3.83 g 4-methylpyridazine in 40 mL THF at -70° and stirred at room temperature, followed by adding a solution of 6.84 g Et 4-fluorobenzoate in 40 mL THF at -70°, and the resulting mixture was stirred at room temperature for 3 h to give 40% 1-fluoro-4-(4-pyridazinylacetyl)benzene (II). To a solution of 4 g II in 80 mL THF was added 4.41 g N,N-dimethylformamide di-Me acetal and stirred at room temperature for 20 h, followed by distilling off the solvent under reduced pressure, and the residue was dissolved in 60 mL ethanol, treated with 1.85 g hydrazine monohydrate, and stirred at 50° for 30 min to give 79% 3(5)-(4-fluorophenyl)-4-(4-pyridazinyl)pyrazole (III). In a p38MAP kinase-binding inhibitory assay, III in vitro showed IC50 of 6.5 nM for inhibiting the binding of a radioligand, [3H]-SB202190, i.e. 4-(4-fluorophenyl)-2-(4-hydroxy-3,4-di-3H-phenyl)-5-(4-pyridyl)imidazole, on cytosol of human monocyte THP-1 cell. III at 30 mg/kg in vivo inhibited the lipopolysaccharide (**LPS**)-induced production of TNF-α in mice by 84% after 6 h.

L18 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN

2002:315096 Document No. 136:320419 Human IL-17-related protein LP-48 and therapeutic use thereof. Glasebrook, Andrew Lawrence; Liu, Ling; Newton, Christy Michelle; Tetreault, Jonathan Wendell (Eli Lilly and Company, USA). PCT Int. Appl. WO 2002033083 A2 20020425, 112 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US27737 20010928. PRIORITY: US 2000-PV240177 20001013; US 2001-PV309936 20010803.

AB The invention provides protein and cDNA sequences for a novel human IL-17-related protein called LP-48 (also known as IL-17C and IL-21), which is a member of interleukin superfamily. The transgenic mice expressing LP-48 are used to test the function of LP-48 and possible therapeutic applications. LP-48 can protect the transgenic mice against **LPS** -induced septic shock and from **LPS**-induced death. LP-48 protein can inhibit **LPS**-induced increases in IFN-γ, IL-12,

TNF-α and IL-6 secretion in transgenic mice. LP-48 can reduce apoptosis in human endothelial cells, more specifically, apoptosis induced by staurosporine. LP-48 can bind to the cell surface of endothelial cells and other tissues specifically through natural LP-48 receptors. Methods are provided for the **treatment** or prevention of atherosclerosis, allergic autoimmune diseases, endothelial cell apoptosis, allograft vasculopathy, hypertension, congestive **heart failure**, ischemia/reperfusion injury, type 1 diabetes, inflammation, immunodeficiencies, cancers, and infectious diseases by administering a human IL-17 related polypeptide and/or an antibody recognizing an epitope thereof to a patient in need of such therapy.

L18 ANSWER 5 OF 11 MEDLINE on STN

2002092665. PubMed ID: 11744024. Endotoxin induces desensitization of cardiac endothelin-1 receptor signaling by increased expression of RGS4 and RGS16. Patten Monica; Bunemann Jan; Thoma Bryan; Kramer Elisabeth; Thoenes Martin; Stube Sabine; Mittmann Clemens; Wieland Thomas. (Medizinische Klinik, Abteilung fur Kardiologie, Universitats-Krankenhaus Hamburg Eppendorf, Martinistr. 52, 20246 Hamburg, FRG.. patten@uke.uni-hamburg.de) . Cardiovascular research, (2002 Jan) 53 (1) 156-64. Journal code: 0077427. ISSN: 0008-6363. Pub. country: Netherlands. Language: English.

AB OBJECTIVE: Endotoxin (**LPS**)-induced **acute** cardiac failure during sepsis is associated with alterations in G protein mediated signal transduction. We therefore examined the expression of the G proteins G(i), G(q), and G(s) and of four 'regulators of G protein signaling' (RGS) proteins, RGS1, RGS4, RGS5, and RGS16 in rat hearts. METHODS: For in vivo experiments, Wistar rats were treated with 600 microg/day E. coli **LPS**, intravenously) and hearts were excised after 6, 24 and 72 h. Cultured neonatal rat cardiomyocytes were treated with 4 microg/ml **LPS** for 24 and 72 h. Isolated membrane proteins were used for Western blot analysis and for evaluation of phospholipase C (PLC) activity. RGS16 mRNA was detected by RNAse protection. RESULTS: **LPS** induced G(i) protein 1.4-fold 72 h after in vivo administration of **LPS**, whereas expression of G(s) and G(q) was unaltered. After 6 h of **LPS treatment**, RGS16 mRNA was transiently up-regulated 3.7-fold, followed by transient protein induction (24 h: 2.5-fold; 72 h: 1.5-fold). Similarly, RGS4 protein was transiently induced (24 h: 3.1-fold; 72 h: 1.5-fold), whereas expression of RGS1 and RGS5 was not altered. Similar to the **LPS** -treated rat hearts, RGS16 expression was transiently induced by **LPS** in cultured neonatal rat cardiomyocytes (24 h: 1.6-fold, 72 h: 0.9-fold). To determine the functional consequences of the RGS protein induction phospholipase C (PLC) activity was analyzed in membranes obtained from solvent and **LPS**-treated hearts. Basal and endothelin-1-stimulated PLC activity was transiently repressed by **LPS** with a maximum after 24 h although no apparent changes in PLCbeta1 or endothelin receptor expression could be detected. CONCLUSION: These data suggest that the rapid up-regulation of cardiac RGS4 and RGS16 is associated with a desensitization of endothelin-1 receptor signaling. Up-regulation of these RGS proteins may thus be involved in the early onset of cardiac failure during sepsis.

L18 ANSWER 6 OF 11 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2001:351619 The Genuine Article (R) Number: 426CF. Wogonin, baicalin, and baicalein inhibition of inducible nitric oxide synthase and cyclooxygenase-2 gene expressions induced by nitric oxide synthase inhibitors and lipopolysaccharide. Chen Y C; Shen S C; Chen L G; Lee T J F; Yang L L (Reprint). Taipei Med Univ, Grad Inst Pharmacognosy Sci, 250 Wu Hsing St, Taipei, Taiwan (Reprint); Taipei Med Univ, Grad Inst Pharmacognosy Sci, Taipei, Taiwan; Taipei Med Univ, Sch Med, Dept Dermatol, Taipei, Taiwan; So Illinois Univ, Sch Med, Dept Pharmacol, Springfield, IL 62794 USA; Natl Chiayi Univ, Life Sci Coll, Grad Inst Biotechnol, Chiayi, Taiwan. BIOCHEMICAL PHARMACOLOGY (1 JUN 2001) Vol. 61, No. 11, pp. 1417-1427. Publisher: PERGAMON-ELSEVIER SCIENCE LTD. THE

BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND. ISSN: 0006-2952. Pub. country: Taiwan; USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We previously reported that oroxylin A, a polyphenolic compound, was a potent inhibitor of lipopolysaccharide (**LPS**)-induced expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). In the present study, three oroxylin A structurally related polyphenols isolated from the Chinese herb Huang Qui, namely baicalin, baicalein, and wogonin, were examined for their effects on **LPS**-induced nitric oxide (NO) production and iNOS and COX-2 gene expressions in RAW 264.7 macrophages. The results indicated that these three polyphenolic compounds inhibited **LPS**-induced NO production in a concentration-dependent manner without a notable cytotoxic effect on these cells. The decrease in NO production was in parallel with the inhibition by these polyphenolic compounds of **LPS**-induced iNOS gene expression. However, these three compounds did not directly affect iNOS enzyme activity. In addition, wogonin, but not baicalin or baicalein, inhibited **LPS**-induced prostaglandin E, (PGE,) production and COX-2 gene expression without affecting COX-2 enzyme activity. Furthermore, N-nitro-L-arginine (NLA) and N-nitro-L-arginine methyl ester (L-NAME) pretreatment enhanced **LPS** -induced iNOS (but not COX-2) protein expression, which was inhibited by these three polyphenolic compounds. Wogonin, but not baicalin or baicalein, similarly inhibited PGE, production and COX-2 protein expression in NLA/**LPS** or L-NAME/**LPS**-co-treated RAW 264.7 cells. These results indicated that co-**treatment** with NOS inhibitors and polyphenolic compounds such as wogonin effectively blocks **acute** production of NO and, at the same time, inhibits expression of iNOS and COX-2 genes. (C) 2001 Elsevier Science Inc. All rights reserved.

L18 ANSWER 7 OF 11 MEDLINE on STN

2001572935. PubMed ID: 11680626. Endotoxin and cytokines alter contractile protein expression in cardiac myocytes in vivo. Patten M; Kramer E; Bunemann J; Wenck C; Thoenes M; Wieland T; Long C. (Medizinische Klinik, Abteilung fur Kardiologie, Universitats-Krankenhaus Hamburg Eppendorf, Hamburg, Germany.. patten@uke.uni-hamburg.de) . Pflugers Archiv : European journal of physiology, (2001 Sep) 442 (6) 920-7. Journal code: 0154720. ISSN: 0031-6768. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB Release of bacterial endotoxin and cytokines induce cardiac failure during sepsis. We investigated the direct effects of E. coli endotoxin (lipopolysaccharide, **LPS**) and cytokines induced by **LPS** on the cardiac myocyte gene program. For in vivo-experiments adult Wistar rats were given 600 microg/day **LPS** i.v. for 24 h or 7 days. In addition, cultured adult rat cardiac myocytes were treated with **LPS**, interleukin-1beta (IL-1beta), tumour necrosis factor-alpha (TNFalpha), interferon-gamma (IFNgamma) or IL-6 for 24 h. mRNA expression was evaluated for cardiac-alpha-actin (cAct), skeletal-alpha-actin (skAct), beta- and alpha-myosin heavy chain (MHC). **LPS** induced betaMHC-mRNA 3.6-fold and repressed alphaMHC 2.7-fold and cAct 2.5-fold after 24 h in vivo. Up-regulation of betaMHC (3-fold) and repression of cAct (2.5-fold) were still observed after 7 days **LPS** infusion, whereas alphaMHC-mRNA levels had returned to normal. At the protein level, increased expression of betaMHC by **LPS treatment** occurred already after 24 h and was maintained thereafter. **LPS** had no influence on skAct-mRNA. Similar changes in contractile protein mRNA expression were observed in **LPS**-treated cardiomyocytes in culture, whereas the tested cytokines either activated (IL-1beta, IFNgamma) or repressed (TNFalpha, IL-6) both MHC-isoforms and cAct. In conclusion, **LPS** and proinflammatory cytokines induce changes in contractile protein expression that may contribute to the **acute heart failure** observed during endotoxaemia.

L18 ANSWER 8 OF 11 EMBASE on STN

2001087660 EMBASE Protective effects of yangambin on cardiovascular hyporeactivity to catecholamines in rats with endotoxin-induced shock.
Araujo C.V.; Barbosa-Filho J.M.; Cordeiro R.S.B.; Tibirica E.. E. Tibirica, Depto. de Fisiologia/Farmacodinamica, Instituto Oswaldo Cruz, FIOCRUZ, Av. Brasil 4365-Manguinhos, 21045-900 Rio de Janeiro, RJ, Brazil. etibi@ioc.fiocruz.br. Naunyn-Schmiedeberg's Archives of Pharmacology 363/3 (267-275) 2001.
Refs: 48.
ISSN: 0028-1298. CODEN: NSAPCC. Pub. Country: Germany. Language: English.
Summary Language: English.

AB The protective effects of a new, selective, plant-derived platelet-activating factor (PAF) antagonist, yangambin, on the cardiovascular alterations and mortality due to endotoxic shock were investigated in anaesthetized rats. We also studied the involvement of PAF in the induction of the vascular and cardiac hyporesponsiveness to adrenergic stimulation observed during endotoxaemia. The animals were sensitized to the lethal effects of Escherichia coli lipopolysaccharide (**LPS**) with D(+)-galactosamine (50 mg/kg, i.v.) 15 min before **LPS** injection. **LPS** (3 mg/kg, i.v.) induced a progressive and marked decrease in mean arterial blood pressure from 85±4 to 30±3 mmHg and a reduction of cardiac output (CO) from 180±7 to 37±3 ml/min (120 min) accompanied by a maintenance of systemic vascular resistance, suggesting that cardiovascular collapse resulted mainly from myocardial depression. The maximum pressor responses to noradrenaline (0.3-3.0 μg/kg, i.v.) fell from 72±9 (control) to 5±1 mmHg (**LPS**) while the CO responses decreased from 81±5 to 8±3 ml/min. Pre-**treatment** with yangambin (30 mg/kg, i.v.) or with WEB 2086 (5 mg/kg, i.v.), a reference PAF receptor antagonist, completely prevented the **LPS**-induced cardiovascular collapse and abolished the sharp reductions of the arterial blood pressure and CO responses to noradrenaline observed during endotoxaemia. Post-**treatment** with yangambin 90 min after **LPS** administration did not reverse the arterial hypotension, cardiac failure or cardiovascular hyporesponsiveness to catecholamines. Finally, the **acute** (150 min) survival rates of endotoxic shock increased from 0% (**LPS** group) to 100% in the groups pretreated with either yangambin or WEB 2086. The long-term (7-day) survival also increased from 0% (**LPS** group) to 85% (yangambin pre-**treatment** group). In conclusion, these data suggest a role for PAF in the pathogenesis of endotoxin-induced vascular and cardiac hyporesponsiveness to catecholamines and confirm its involvement in the complex cascade of multiple mediators released during endotoxic/septic shock. Yangambin proved to be an effective pharmacological agent against cardiovascular collapse and mortality in endotoxin shock.

L18 ANSWER 9 OF 11 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:437776 The Genuine Article (R) Number: 202TG. Endotoxin and immune activation in chronic **heart failure**: a prospective cohort study. Niebauer J; Volk H D; Kemp M; Dominguez M; Schumann R R; Rauchhaus M; PooleWilson P A; Coats A J S; Anker S D (Reprint). NATL HEART & LUNG INST, IMPERIAL COLL SCH MED, DOVEHOUSE ST, LONDON SW3 6LY, ENGLAND (Reprint); NATL HEART & LUNG INST, IMPERIAL COLL SCH MED, LONDON SW3 6LY, ENGLAND; UNIV LEIPZIG, HERZZENTRUM, LEIPZIG, GERMANY; UNIV KLINIKUM CHARITE, INST MED IMMUNOL, BERLIN, GERMANY; HAREFIELD HOSP, HEART SCI CTR, HAREFIELD, MIDDX, ENGLAND; UNIV KLINIKUM CHARITE, INST MIKROBIOL & HYG, BERLIN, GERMANY; MAX DELBRUCK CTR MOL MED, FRANZ VOLHARD KLIN, BERLIN, GERMANY. LANCET (29 MAY 1999) Vol. 353, No. 9167, pp. 1838-1842.
Publisher: LANCET LTD. 42 BEDFORD SQUARE, LONDON WC1B 3SL, ENGLAND. ISSN: 0140-6736. Pub. country: ENGLAND; GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background. Immune activation in patients with chronic **heart failure** may be secondary to endotoxin (lipopolysaccharide) action. We investigated the hypothesis that altered gut permeability with bacterial translocation and endotoxaemia would be increased in patients with oedema secondary to congestive **heart failure.**
Methods. We compared 20 patients who had chronic **heart**

failure with recent-onset peripheral oedema (mean age 64 years [SD 10], New York Heart Association [NYHA] class 3.3 [0.7]), 20 stable non-oedematous patients with chronic **heart failure** (mean age 63 years [19], NYHA class 2.6 [0.7]), and 14 healthy volunteers (mean age 55 years [16]). Biochemical markers of endotoxaemia, inflammation, and immune activation were measured. Ten patients were studied within 1 week of complete resolution of oedema. Five patients survived longer than 6 months and were restudied again after remaining free of oedema for more than 3 months.

Findings. Mean endotoxin concentrations were higher in oedematous patients with chronic **heart failure** than in stable patients with chronic **heart failure** (0.74 [SD 0.45] vs 0.37 EU/mL [0.23], p = 0.0009) and controls (0.46 EU/mL [0.21], p = 0.02). Oedematous patients had the highest concentrations of several cytokines. After short-term diuretic **treatment**, endotoxin concentrations decreased from 0.84 EU/mL [0.49] to 0.45 EU/mL [0.21], p < 0.05) but cytokines remained raised. After freedom of oedema for more than 3 months after oedema resolved, endotoxin concentrations remained unchanged from the previous visit (0.49 EU/mL [0.06], p = 0.45).

Interpretation. Raised concentrations of endotoxin and cytokines are found in patients with chronic **heart failure** during **acute** oedematous exacerbation. Intensified diuretic **treatment** can normalise endotoxin concentrations. Our preliminary findings suggest that endotoxin may trigger immune activation in patients with chronic **heart failure** during oedematous episodes.

L18 ANSWER 10 OF 11 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

1999:871285 The Genuine Article (R) Number: 253ME. Transvenous parasympathetic cardiac nerve stimulation: An approach for stable sinus rate control. Schauerte P N; Scherlag B J (Reprint); Scherlag M A; Goli S; Jackman W; Lazzara R. UNIV OKLAHOMA, HLTH SCI CTR, DVA MED CTR, RES SERV 151F, 921 NE 13TH ST, OKLAHOMA CITY, OK 73104 (Reprint); UNIV OKLAHOMA, HLTH SCI CTR, DEPT INTERNAL MED, CARDIOVASC SECT, OKLAHOMA CITY, OK; DEPT VET AFFAIRS MED CTR, OKLAHOMA CITY, OK. JOURNAL OF CARDIOVASCULAR ELECTROPHYSIOLOGY (NOV 1999) Vol. 10, No. 11, pp. 1517-1524. Publisher: FUTURA PUBL CO. 135 BEDFORD RD, PO BOX 418, ARMONK, NY 10504-0418. ISSN: 1045-3873. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Introduction: Epicardial electrical stimulation of parasympathetic nerves innervating the sinus node has been shown to decrease sinus rate. We investigated whether intravascular parasympathetic cardiac nerve stimulation (IPS) can be achieved over a relatively long-term period to slow the supraventricular rate.

Methods and Results: Fifteen dogs were investigated. IFS was performed with rectangular stimuli (0.05-msec duration, 20 Hz) using a catheter with an expandable electrode basket. The catheter was positioned in the superior vena cava (SVC; n = 9) or right pulmonary artery (RPA; n = 6), The basket then was expanded to hold the catheter in place. Nonfluoroscopic identification of effective IFS sites was achieved within 5 minutes in the SVC, Increasing IFS voltage resulted in a graded response of supraventricular rate slowing. A 50% prolongation of the baseline atrial cycle length was achieved with 28 V in the SVC (1,056 +/- 355 msec vs 489 +/- 154 msec; P < 0.001) and 25 V in the RPA (1,181 +/- 306 msec vs 518 +/- 138 msec; P < 0.01), The rate slowing started immediately after IFS onset, terminated abruptly after IFS cessation, and could be maintained over 10 hours. A rate slowing effect also was observed when the sinus rate was increased by isoproterenol (SVC: 304 +/- 8 msec/RPA: 341 +/- 9 msec with isoproterenol vs SVC: 635 +/- 12 msec with isoproterenol + **LPS** at 39 V/ RPA: 584 +/- 16 msec with isoproterenol + TPS at 38 V; n = 6).

Conclusion: IFS results in a significant supraventricular rate slowing that is stable over a relatively long period and may be applied to slow undesirable sinus tachycardia in **acute** ischemic syndromes or to counteract undesirable chronotropic effects of catecholamines during **treatment** of cardiogenic or septic shock and **acute**

congestive **heart failure.**

L18 ANSWER 11 OF 11 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:65114 The Genuine Article (R) Number: 155LC. **LPS**-Induced TNF-alpha release from and apoptosis in rat cardiomyocytes: Obligatory role for CD14 in mediating the **LPS** response. Comstock K L; Krown K A (Reprint); Page M T; Martin D; Ho P; Pedraza M; Castro E N; Nakajima N; Glembotski C C; Quintana P J E; Sabbadini R A. REES STEALY RES FDN, 2001 4TH AVE, SAN DIEGO, CA 92101 (Reprint); REES STEALY RES FDN, SAN DIEGO, CA 92101; SAN DIEGO STATE UNIV, DEPT BIOL, SAN DIEGO, CA 92182; SAN DIEGO STATE UNIV, GRAD SCH PUBL HLTH, SAN DIEGO, CA 92182. JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY (DEC 1998) Vol. 30, No. 12, pp. 2761-2775. Publisher: ACADEMIC PRESS LTD. 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND. ISSN: 0022-2828. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The bacterial endotoxin lipopolysaccharide (**LPS**) contributes to the cardiovascular collapse and death observed in patients with sepsis. Because **LPS** has such profound effects on cardiac performance, we speculate that direct effects of **LPS** could be demonstrated on cardiomyocytes in culture, and that these direct effects are mediated by the **LPS** receptor, CD14. Accordingly, in this study, we provide evidence for CD14-dependent cardiotoxic effects of **LPS** including the **LPS**-stimulated secretion of tumor necrosis factor alpha (TNF-alpha) from cardiomyocytes. TNF-alpha is an inflammatory cytokine which is renown for its negative inotropic effects on cardiac performance, but has not until recently been shown to be produced by cardiac cells. In this study, **LPS** was found to stimulate strongly in a dose-dependent manner the secretion of TNF-alpha from cultured adult rat cardiomyocytes. Further, **LPS**-induced TNF-alpha secretion was blocked by an inhibitor of TNF-alpha processing metallomatrix protease inhibitor (TAPI). Molecular and immulogical evidence demonstrated the presence of **LPS** receptors (CD14) on cardiomyocytes. Attenuated TNF-alpha secretion following PI-PLC **treatment** confirmed the functional importance of CD14 for **LPS**-mediated myocardial effects. Importantly, **LPS** also triggered apoptosis in cultured cardiomyocytes as quantified by single-cell gel electrophoresis of nuclei exhibiting DNA fragmentation patterns characteristic of apoptosis (i.e. cardiac comets). Apoptotic cell death was blocked by pre-incubation with the soluble TNF-alpha receptor fragment (TNFRII:Fc), suggesting that **LPS**-induced apoptosis was TNF-alpha-dependent and probably involved an autocrine function for the TNF-alpha whose secretion was under **LPS** control. The results of this study suggest that the cardiodepressant effects of **LPS** are dependent on CD14 signaling and may not only be due to **acute** negative inotropic effects of TNE-alpha but also may be complicated by TNF-alpha-induced apoptotic cell death which effectively reduces the number of working myocardial cells.
(C) 1998 Academic Press.

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=> s (anker s?/au or coats a?/au or volk h?/au or rauchhaus m?/au or schumann r?/au)
L19        6453 (ANKER S?/AU OR COATS A?/AU OR VOLK H?/AU OR RAUCHHAUS M?/AU OR
                SCHUMANN R?/AU)

=> s l19 and LPS
L20         309 L19 AND LPS

=> s l20 and heart failure
L21          19 L20 AND HEART FAILURE

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PROCESSING COMPLETED FOR L21
L22          11 DUP REMOVE L21 (8 DUPLICATES REMOVED)

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L22 ANSWER 1 OF 11 MEDLINE on STN DUPLICATE 1
2004283437. PubMed ID: 15182775. Selective intestinal decontamination in advanced chronic **heart failure**: a pilot trial.
Conraads Viviane M; Jorens Philippe G; De Clerck Luc S; Van Saene Hendrik K; Ieven Margaretha M; Bosmans Johan M; Schuerwegh Annemie; Bridts Chris H; Wuyts Floris; Stevens Wim J; **Anker Stefan D**; **Rauchhaus Mathias**; Vrints Christiaan J. (Department of Cardiology, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium.) European journal of heart failure : journal of the Working Group on Heart Failure of the European Society of Cardiology, (2004 Jun) 6 (4) 483-91. Journal code: 100887595. ISSN: 1388-9842. Pub. country: Netherlands. Language: English.

AB Background and aims: Endotoxin, derived from intestinal aerobic Gram-negative bacilli (AGNB), could be an important monocyte activator in chronic **heart failure** (CHF). The effect of selective decontamination of the digestive tract (SDD) on intracellular monocyte cytokine production, monocyte CD14 expression, circulating endotoxin and cytokines, and flow-mediated dilation (FMD) was studied in patients with severe CHF. Methods and results: Ten patients with CHF (NYHA class III-IV) were enrolled in a non-placebo controlled pilot trial involving the administration of SDD (polymyxin B, tobramycin) for 8 weeks. One patient was later excluded due to cardiac transplantation. Before treatment, after 4 and 8 weeks therapy, and 6 weeks post-treatment, monocyte CD14 expression, intracellular monocyte production of interleukin-1beta [IL-1beta], interleukin-6 [IL-6], tumour necrosis factor (TNF)-alpha with and without lipopolysaccharide (**LPS**) stimulation were measured. Concentrations of endotoxin and cytokines (IL-1beta, IL-6, TNF-alpha) were also determined. AGNB in faeces, intestinal endotoxin and FMD were assessed at baseline, after 4 weeks of treatment and 6 weeks post-treatment. SDD eradicated intestinal AGNB ($P<0.00001$) and decreased faecal endotoxin concentrations ($P<0.00001$). There was a significant decline in monocyte CD14 expression ($P=0.03$) and in IL-1beta ($P=0.0001$), IL-6 ($P=0.02$) and TNF-alpha ($P=0.0002$) production after 4 and 8 weeks of treatment in the basal state and for IL-1beta ($P=0.008$) and IL-6 ($P=0.005$) after **LPS** stimulation. FMD significantly improved at 4 weeks and returned to baseline after treatment discontinuation ($P=0.002$). Circulating concentrations of endotoxin and cytokines remained unchanged. Conclusion: Reduction of the intestinal endotoxin pool led to a decrease in monocyte CD14 expression and intracellular cytokine production in patients with severe CHF. The improvement of peripheral endothelial function could be a marker of the anti-inflammatory effect of SDD.

L22 ANSWER 2 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2004:50571 Document No.: PREV200400049667. Endotoxin inhibits apoptosis in ex vivo mononuclear blood cells from patients with chronic **heart failure.** Jankowska, E. A. [Reprint Author]; Gutherc, R.; Kus-Klinowska, A. [Reprint Author]; von Haehling, S.; Banasiak, W. [Reprint Author]; **Anker, S.**; Ponikowski, P. [Reprint Author]. Cardiac Department, Military Hospital, Wroclaw, Poland. European Heart Journal, (August-September 2003) Vol. 24, No. Abstract Supplement, pp. 611. print.
Meeting Info.: Congress of the European Society of Cardiology. Vienna, Austria. August 30-September 03, 2003. European Society of Cardiology. ISSN: 0195-668X (ISSN print). Language: English.

L22 ANSWER 3 OF 11 MEDLINE on STN DUPLICATE 2
2003418140. PubMed ID: 12957752. The relationship between age and production of tumour necrosis factor-alpha in healthy volunteers and patients with chronic **heart failure.** von Haehling Stephan; Genth-Zotz Sabine; Sharma Rakesh; Bolger Aidan P; Doehner Wolfram; Barnes Peter J; **Coats Andrew J S**; **Anker Stefan D.** (Department of Clinical Cardiology, National Heart and Lung Institute, London SW3 6LY, UK.. stephan.von.haehling@web.de) . International journal of cardiology, (2003 Aug) 90 (2-3) 197-204. Journal

code: 8200291. ISSN: 0167-5273. Pub. country: Ireland. Language: English.

AB BACKGROUND: Ageing is associated with an altered immune response. Elevated plasma levels of tumour necrosis factor-alpha (TNF-alpha) are present in patients with advanced chronic **heart failure** (CHF). However, the relationship between age and the immune response in CHF is unknown. METHODS: We investigated the relationship between age and the TNF-alpha generating capacity of lipopolysaccharide (**LPS**) stimulated peripheral blood mononuclear cells (PBMC) in nine healthy control subjects (mean age 51.6+/-3.6 years, age range 39-75 years) and 22 stable patients with CHF (mean age 68.3+/-1.5 years, age range 52-78 years, NYHA class 3.0+/-0.2). We also tested the TNF-alpha generating capacity of all control subjects and 18 CHF patients in whole blood cultures. RESULTS: Subjects were subgrouped according to baseline TNF-alpha secretion in PBMC cultures into low- and high-responders, with the latter producing TNF-alpha even without **LPS** stimulation. High-responders produced more TNF-alpha than low-responders at all **LPS** doses (0.001-10 ng/ml, P<0.0001, repeated measures ANOVA), and high-responders were significantly older than low-responders (controls: 65.8+/-9.2 vs. 47.5+/-2.5 years; patients: 71.9+/-1.9 vs. 65.9+/-1.9 years, both P<0.05). Age correlated with TNF-alpha production in both patients and controls. This effect was independent of NYHA class. CONCLUSIONS: **LPS**-responsiveness appears to relate to age in both healthy controls and CHF patients. When assessing the immune status of CHF patients, age should therefore be considered an important confounding factor. In whole blood these findings could only be confirmed at the highest **LPS** concentration used, thus suggesting that certain factors in the blood may be able to abolish **LPS** activity at lower concentrations.

L22 ANSWER 4 OF 11 MEDLINE on STN DUPLICATE 3

2002406358. PubMed ID: 12161227. Effect of interleukin-10 on the production of tumor necrosis factor-alpha by peripheral blood mononuclear cells from patients with chronic **heart failure.** Bolger Aidan P; Sharma Rakesh; von Haehling Stephan; Doehner Wolfram; Oliver Brian; **Rauchhaus Mathias**; **Coats Andrew J S**; Adcock Ian M; **Anker Stefan D.** (Clinical Cardiology, National Heart and Lung Institute, Imperial College School of Medicine, London, United Kingdom.. a.bolger@ic.ac.uk) . American journal of cardiology, (2002 Aug 15) 90 (4) 384-9. Journal code: 0207277. ISSN: 0002-9149. Pub. country: United States. Language: English.

AB Chronic **heart failure** (HF) is a state of inflammatory immune activation characterized by elevated circulating levels of tumor necrosis factor-alpha (TNF-alpha). Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine that inhibits TNF-alpha production and lessens endotoxin bioactivity. It is not known whether IL-10 reduces lipopolysaccharide (**LPS**) stimulated TNF-alpha production of peripheral blood mononuclear cells (PBMCs) from patients with chronic HF. PBMCs were isolated from 15 patients with chronic HF (New York Heart Association functional class 3.0 +/- 0.2, left ventricular ejection fraction 30 +/- 2%, peak oxygen consumption 18.1 +/- 0.8 ml/kg/min) and 15 healthy control subjects and stimulated with 1 and 10 ng/ml **LPS** for 24 hours with or without prior addition of IL-10 (10 ng/ml). TNF-alpha was quantified in cell-free supernatants by an enzyme-linked immunosorbent assay. TNF-alpha, soluble TNF receptors, IL-10, and **LPS** were quantified in plasma. **LPS** stimulated TNF-alpha production was highest in those patients in New York Heart Association class II (p <0.01 vs New York Heart Association class III and IV, p <0.001 vs control subjects). IL-10 reduced PBMC TNF-alpha production in all stimulated samples at 1 and 10 ng/ml **LPS** (mean reduction 43% at 1 ng/ml, p <0.01 and 55% at 10 ng/ml, p <0.0001). The percentage reduction in TNF-alpha release did not differ significantly between patients and control subjects or with respect to severity of chronic HF or baseline immune parameters. Independently of clinical severity, IL-10 profoundly inhibits TNF-alpha release from PBMCs isolated from patients with chronic HF. IL-10 is, therefore, a potential therapy for use in

chronic HF associated with inflammatory immune activation.

L22 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2001:811003 Document No. 136:384011 Antiendotoxin antibody levels in unstable angina: lessons from chronic **heart failure** and cardiopulmonary bypass. Bolger, Aidan P.; Rashid, Mohammed; **Anker, Stefan D.** (London, UK). American Journal of Cardiology, 88(10), 1217 (English) 2001. CODEN: AJCDAG. ISSN: 0002-9149. Publisher: Excerpta Medica, Inc..
AB A polemic to Kahler et al. (Am. J. Cardiol., Volume 87, 2001, 1150-1153) on cardiovascular events associated with changes in antibodies directed against endotoxin. Exposure to endotoxin (lipopolysaccharide or **LPS**) is a feature of both cardiopulmonary bypass (CPB) and severe chronic **heart failure** (CHF). Patients with severe CHF, i.e., those known to have high circulating **LPS** levels, had significantly lower IgM titers than other **heart failure** classes of healthy controls. The same results were observed with regard to IgG. It was proposed that unstable angina, particularly when associated with systemic hypotension, is a candidate state for gut-derived endotoxemia. This would also apply to acute myocardial infarction.

L22 ANSWER 6 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2001:222991 Document No.: PREV200100222991. Endotoxin and severity of chronic **heart failure. Rauchhaus, Mathias** [Reprint author]; Doehner, Wolfram; Bolger, Aidan; Sharma, Rakesh; Schmidt, Hendrik; Davos, Constantinos; Kemp, Michael; **Coats, Andrew J. S.** ; **Anker, Stefan D.**. Clinical Cardiology, NHLI, London, UK. Journal of the American College of Cardiology, (February, 2001) Vol. 37, No. 2 Supplement A, pp. 190A. print.
Meeting Info.: 50th Annual Scientific Session of the American College of Cardiology. Orlando, Florida, USA. March 18-21, 2001. American College of Cardiology.
CODEN: JACCDI. ISSN: 0735-1097. Language: English.

L22 ANSWER 7 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2001:222992 Document No.: PREV200100222992. Evidence of endotoxin exposure in patients with severe chronic **heart failure** by determination of antiendotoxin core antibody levels. Bolger, Aidan P. [Reprint author]; Rashid, Mohammed [Reprint author]; Sharma, Rakesh [Reprint author]; **Rauchhaus, Mathias** [Reprint author]; Doehner, Wolfram [Reprint author]; Stephens, Robert [Reprint author]; Barclay, Robin [Reprint author]; **Coats, Andrew J. S.** [Reprint author]; **Anker, Stephan D.** [Reprint author]. National Heart and Lung Institute, London, UK. Journal of the American College of Cardiology, (February, 2001) Vol. 37, No. 2 Supplement A, pp. 190A. print.
Meeting Info.: 50th Annual Scientific Session of the American College of Cardiology. Orlando, Florida, USA. March 18-21, 2001. American College of Cardiology.
CODEN: JACCDI. ISSN: 0735-1097. Language: English.

L22 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2000:645885 Document No. 133:217694 Endotoxin-modulating compounds for therapy of **heart failure** and cachexia. **Anker, Stefan; Coats, Andrew; Volk, Hans-Dieter; Rauchhaus, Mathias; Schumann, Ralf Reiner** (Max-Delbruck-Centrum fur Molekulare Medizin, Germany). PCT Int. Appl. WO 2000053224 A2 20000914, 74 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP2299 20000309. PRIORITY: GB 1999-5300 19990309; GB 1999-5307

19990309; GB 1999-5310 19990309; GB 1999-5314 19990309; GB 1999-5315 19990309.

AB A method of treating, preventing or ameliorating chronic or acute **heart failure** in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; **LPS**) mol., e.g. **LPS** binding protein, BPI, lipoproteins, bile acids, or an antibody capable of binding **LPS**, a compound that is able to bind to an endotoxin (lipopolysaccharide; **LPS**) mol. or bacterium in the gut, e.g. charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; **LPS**), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (**LPS**) from the gut into the patient's circulation. A method of treating, preventing or ameliorating endotoxin-mediated immune activation in acute or chronic **heart failure** in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; **LPS**) mol., e.g. **LPS** binding protein, BPI, lipoproteins, bile acids or an antibody capable of binding **LPS**, a compound that is able to bind to an endotoxin (lipopolysaccharide; **LPS**) mol. or bacterium in the gut, e.g. charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; **LPS**), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (**LPS**) from the gut into the patient's circulation. Also disclosed is a method for treating cachexia and wasting syndromes due to diseases other than congestive **heart failure.**

L22 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN

2000:645835 Document No. 133:217707 Therapy of cachexia and wasting syndromes with bile acids. **Anker, Stefan; Coats, Andrew ; Volk, Hans-dieter; Schumann, Ralf Reiner**; Plauth, Mathias; Lochs, Herbert (Max-Delbruck-Centrum fur Molekulare Medizin, Germany). PCT Int. Appl. WO 2000053165 A2 20000914, 26 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP2062 20000309. PRIORITY: GB 1999-5315 19990309; GB 1999-5300 19990309; GB 1999-5310 19990309; GB 1999-5307 19990309; GB 1999-5314 19990309.

AB The present invention relates to therapy and the use of agents in the therapy of cachexia and wasting syndromes due to diseases other than congestive **heart failure.** Cachexia occurs in a number of other chronic diseases, like liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, and rheumatoid arthritis. Cachexia and weight loss are linked to inflammatory processes and they are linked to increased mortality and/or morbidity. Cytokine activation is a potential causal mechanism for the development of cachexia also in these other diseases. The invention describes a method of treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis in a patient. The method comprises administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; **LPS**). The invention describes also a method of treating, preventing or ameliorating endotoxin-mediated immune activation in body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes,

rheumatoid arthritis. The method comprises administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; **LPS**). The ability of ursodeoxycholic acid and BPI protein to inhibit LPD-mediated NFT production in the whole blood of patients with cachexia is shown.

L22 ANSWER 10 OF 11 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:437776 The Genuine Article (R) Number: 202TG. Endotoxin and immune activation in chronic **heart failure**: a prospective cohort study. Niebauer J; **Volk H D**; Kemp M; Dominguez M; **Schumann R R**; **Rauchhaus M**; PooleWilson P A; **Coats A J S**; **Anker S D (Reprint)**. NATL HEART & LUNG INST, IMPERIAL COLL SCH MED, DOVEHOUSE ST, LONDON SW3 6LY, ENGLAND (Reprint); NATL HEART & LUNG INST, IMPERIAL COLL SCH MED, LONDON SW3 6LY, ENGLAND; UNIV LEIPZIG, HERZZENTRUM, LEIPZIG, GERMANY; UNIV KLINIKUM CHARITE, INST MED IMMUNOL, BERLIN, GERMANY; HAREFIELD HOSP, HEART SCI CTR, HAREFIELD, MIDDX, ENGLAND; UNIV KLINIKUM CHARITE, INST MIKROBIOL & HYG, BERLIN, GERMANY; MAX DELBRUCK CTR MOL MED, FRANZ VOLHARD KLIN, BERLIN, GERMANY. LANCET (29 MAY 1999) Vol. 353, No. 9167, pp. 1838-1842. Publisher: LANCET LTD. 42 BEDFORD SQUARE, LONDON WC1B 3SL, ENGLAND. ISSN: 0140-6736. Pub. country: ENGLAND; GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background. Immune activation in patients with chronic **heart failure** may be secondary to endotoxin (lipopolysaccharide) action. We investigated the hypothesis that altered gut permeability with bacterial translocation and endotoxaemia would be increased in patients with oedema secondary to congestive **heart failure.**

Methods. We compared 20 patients who had chronic **heart failure** with recent-onset peripheral oedema (mean age 64 years [SD 10], New York Heart Association [NYHA] class 3.3 [0.7]), 20 stable non-oedematous patients with chronic **heart failure** (mean age 63 years [19], NYHA class 2.6 [0.7]), and 14 healthy volunteers (mean age 55 years [16]). Biochemical markers of endotoxaemia, inflammation, and immune activation were measured. Ten patients were studied within 1 week of complete resolution of oedema. Five patients survived longer than 6 months and were restudied again after remaining free of oedema for more than 3 months.

Findings. Mean endotoxin concentrations were higher in oedematous patients with chronic **heart failure** than in stable patients with chronic **heart failure** (0.74 [SD 0.45] vs 0.37 EU/mL [0.23], p = 0.0009) and controls (0.46 EU/mL [0.21], p = 0.02). Oedematous patients had the highest concentrations of several cytokines. After short-term diuretic treatment, endotoxin concentrations decreased from 0.84 EU/mL [0.49] to 0.45 EU/mL [0.21], p < 0.05) but cytokines remained raised. After freedom of oedema for more than 3 months after oedema resolved, endotoxin concentrations remained unchanged from the previous visit (0.49 EU/mL [0.06], p = 0.45).

Interpretation. Raised concentrations of endotoxin and cytokines are found in patients with chronic **heart failure** during acute oedematous exacerbation. Intensified diuretic treatment can normalise endotoxin concentrations. Our preliminary findings suggest that endotoxin may trigger immune activation in patients with chronic **heart failure** during oedematous episodes.

L22 ANSWER 11 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2000:17408 Document No.: PREV200000017408. Markers of intestinal ischemia relate to immune activation in chronic **heart failure.**
Koloczek, Veronika [Reprint author]; **Rauchhaus, Mathias** [Reprint author]; Crane, Roger; Bjarnanson, Ingvar; Menzies, Ian S.; Kemp, Michael; Holtz, Juergen; Poole-Wilson, Philip A.; **Coats, Andrew J. S.**; **Anker, Stefan D.**. National Heart and Lung Inst, London, UK.
Circulation, (Nov. 2, 1999) Vol. 100, No. 18 SUPPL., pp. I.206-I.207. print.
Meeting Info.: 72nd Scientific Sessions of the American Heart Association.

Atlanta, Georgia, USA. November 7-10, 1999.
CODEN: CIRCAZ. ISSN: 0009-7322. Language: English.

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=> s heart failure
L23      256687 HEART FAILURE

=> s l23 and treatment
L24       69457 L23 AND TREATMENT

=> s l24 and LPS
L25          89 L24 AND LPS

=> s l25 and LPS binding protein
L26           0 L25 AND LPS BINDING PROTEIN

=> dup remove l25
PROCESSING COMPLETED FOR L25
L27          46 DUP REMOVE L25 (43 DUPLICATES REMOVED)

=> s l27 and bile acid
L28           0 L27 AND BILE ACID

=> s l27 and TNF
L29          23 L27 AND TNF

=> dup remove l29
PROCESSING COMPLETED FOR L29
L30          23 DUP REMOVE L29 (0 DUPLICATES REMOVED)

=> d l30 1-23 cbib abs

L30  ANSWER 1 OF 23      MEDLINE on STN
2004237705.    PubMed ID: 15135663.   Cytokines are not upregulated in
     adriamycin-induced cardiomyopathy and heart failure.
     Lou H; Danelisen I; Singal P K. (Institute of Cardiovascular Sciences, St.
     Boniface General Hospital Research Centre, Faculty of Medicine, University
     of Manitoba, Room 3022, 351 Tache Avenue, Winnipeg, Man., Canada R2H 2A6.
     ) Journal of molecular and cellular cardiology, (2004 May) 36 (5) 683-90.
     Journal code: 0262322. ISSN: 0022-2828. Pub. country: England: United
     Kingdom. Language: English.
AB   Heart failure due to a variety of causes is
     accompanied by an upregulation of cytokines, such as tumor necrosis
     factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta) and
     interleukin-6 (IL-6).  Adriamycin-induced cardiomyopathy (AIC) and
     heart failure is an important clinical problem.  The
     current study investigated the expression of these cytokines in AIC and
     heart failure in rats.  Both early and late stages of
     AIC was produced in rats.  Myocardial gene expressions for TNF
     -alpha, IL-1beta and IL-6 were examined with DNA microarrays and RT-PCR.
     Protein levels of these cytokines in both the plasma and the myocardium
     were also examined by ELISA.  In the early stage, myocardial mRNA
     expression of IL-1beta showed significant increase at 4 and 24 h, peaking
     at 4 h, while TNF-alpha did not change and IL-6 was
     undetectable.  The protein levels of these three genes did not show any
     upregulation in the plasma or the heart.  In the late stage, heart
     failure was confirmed by clinical signs as well as homodynamic
     changes.  In this stage, plasma protein levels for TNF-alpha,
     IL-1beta and IL-6 were not changed.  However, myocardial TNF
     -alpha mRNA expression and protein levels were significantly decreased,
     while both IL-1beta mRNA and protein levels were not different compared to
     the control group.  IL-6 mRNA expression was undetectable in both normal
     and adriamycin-treated hearts while its protein level was not changed by
     adriamycin.  Positive control using lipopolysaccharides (LPS)
     treatment (0.5 mg/kg body weight) for 2 h resulted in a
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significant increase in these three cytokines in the heart and plasma. These data suggest that an upregulation of cytokines may not be involved in AIC. **Heart failure** may in fact be accentuated by a downregulation of myocardial **TNF**-alpha.

L30 ANSWER 2 OF 23 MEDLINE on STN
2004283437. PubMed ID: 15182775. Selective intestinal decontamination in advanced chronic **heart failure**: a pilot trial.
Conraads Viviane M; Jorens Philippe G; De Clerck Luc S; Van Saene Hendrik K; Ieven Margaretha M; Bosmans Johan M; Schuerwegh Annemie; Bridts Chris H; Wuyts Floris; Stevens Wim J; Anker Stefan D; Rauchhaus Mathias; Vrints Christiaan J. (Department of Cardiology, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium.) European journal of heart failure : journal of the Working Group on Heart Failure of the European Society of Cardiology, (2004 Jun) 6 (4) 483-91. Journal code: 100887595. ISSN: 1388-9842. Pub. country: Netherlands. Language: English.

AB Background and aims: Endotoxin, derived from intestinal aerobic Gram-negative bacilli (AGNB), could be an important monocyte activator in chronic **heart failure** (CHF). The effect of selective decontamination of the digestive tract (SDD) on intracellular monocyte cytokine production, monocyte CD14 expression, circulating endotoxin and cytokines, and flow-mediated dilation (FMD) was studied in patients with severe CHF. Methods and results: Ten patients with CHF (NYHA class III-IV) were enrolled in a non-placebo controlled pilot trial involving the administration of SDD (polymyxin B, tobramycin) for 8 weeks. One patient was later excluded due to cardiac transplantation. Before **treatment**, after 4 and 8 weeks therapy, and 6 weeks post-**treatment**, monocyte CD14 expression, intracellular monocyte production of interleukin-1beta [IL-1beta], interleukin-6 [IL-6], tumour necrosis factor (**TNF**)-alpha with and without lipopolysaccharide (**LPS**) stimulation were measured. Concentrations of endotoxin and cytokines (IL-1beta, IL-6, **TNF**-alpha) were also determined. AGNB in faeces, intestinal endotoxin and FMD were assessed at baseline, after 4 weeks of **treatment** and 6 weeks post-**treatment.** SDD eradicated intestinal AGNB (P<0.00001) and decreased faecal endotoxin concentrations (P<0.00001). There was a significant decline in monocyte CD14 expression (P=0.03) and in IL-1beta (P=0.0001), IL-6 (P=0.02) and **TNF**-alpha (P=0.0002) production after 4 and 8 weeks of **treatment** in the basal state and for IL-1beta (P=0.008) and IL-6 (P=0.005) after **LPS** stimulation. FMD significantly improved at 4 weeks and returned to baseline after **treatment** discontinuation (P=0.002). Circulating concentrations of endotoxin and cytokines remained unchanged. Conclusion: Reduction of the intestinal endotoxin pool led to a decrease in monocyte CD14 expression and intracellular cytokine production in patients with severe CHF. The improvement of peripheral endothelial function could be a marker of the anti-inflammatory effect of SDD.

L30 ANSWER 3 OF 23 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:509992 The Genuine Article (R) Number: 688AZ. Atrial natriuretic peptide polarizes human dendritic cells toward a Th2-promoting phenotype through its receptor guanylyl cyclase-coupled receptor A. Morita R; Ukyo N; Furuya M; Uchiyama T; Hori T (Reprint). Kyoto Univ, Grad Sch Med, Dept Hematol & Oncol, Sakyo Ku, 54 Shogoin Kawara Cyo, Kyoto 6068507, Japan (Reprint); Kyoto Univ, Grad Sch Med, Dept Hematol & Oncol, Sakyo Ku, Kyoto 6068507, Japan; Suntory Inst Biomed Res, Osaka, Japan. JOURNAL OF IMMUNOLOGY (15 JUN 2003) Vol. 170, No. 12, pp. 5869-5875. Publisher: AMER ASSOC IMMUNOLOGISTS. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. ISSN: 0022-1767. Pub. country: Japan. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Atrial natriuretic peptide (ANP) is a cardiovascular hormone secreted mainly by the cardiac atria and regulates the volume-pressure homeostasis. The action of ANP is mediated by its receptor, guanylyl cyclase-coupled receptor A (GC-A). In this study, we explored the possibility that ANP and GC-A may play a role in the dendritic cell (DC)-mediated immune

regulation. We first examined the expression of GGA in human monocyte-derived DCs in comparison with monocytes and found that DCs but not monocytes express GC-A at both the mRNA and protein levels. DCs responded to ANP with an increase in intracellular cGMP in a dose-dependent manner, indicating that GC-A expressed on DCs is functional. Furthermore, **treatment** of DCs with ANP decreased production of IL-12 and **TNF**-alpha and conversely increased that of IL-10 upon stimulation with **LPS**. In accordance with this change of cytokine production, DCs treated with ANP plus **LPS** promoted differentiation of naive CD4(+) T cells into a Th2 phenotype. Finally, we presented evidence that ANP affected cytokine production of fresh whole blood stimulated with **LPS** in line with the above-mentioned results. These results indicate that ANP polarizes human DCs toward a Th2-promoting phenotype through GC-A and thus can regulate immune responses.

L30 ANSWER 4 OF 23 EMBASE
on STN
2003497219 EMBASE Interleukin-1β mediates endotoxin- and tumor necrosis factor α-induced RGS16 protein expression in cultured cardiac myocytes. Patten M.; Stube S.; Thoma B.; Wieland T.. M. Patten, Zentrum fur Innere Medizin, III, Medizinische Klinik, Univ. Klin. Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. patten@uke.uni-hamburg.de. Naunyn-Schmiedeberg's Archives of Pharmacology 368/5 (360-365) 2003.
Refs: 34.
ISSN: 0028-1298. CODEN: NSAPCC. Pub. Country: Germany. Language: English. Summary Language: English.

AB Endotoxin (**LPS**)-induced cardiac failure is associated with an up-regulation of RGS16 protein expression and repression of phospholipase C activity in vivo. Since the release of pro-inflammatory cytokines plays an important role in mediating **LPS**-induced myocardial dysfunction, we examined the effect of recombinant cytokines on the expression of RGS16 protein in neonatal cardiac myocytes. Myocytes in culture were treated with 50 ng/ml recombinant tumor necrosis factor α (**TNF**.alpha.), 2 ng/ml interleukin 1β (IL-1β), interleukin 6 (IL-6), interferon γ (IFNγ) or diluent (NaCl) for 24 h. Before stimulation with **LPS** (4 μg/ml for 24 h) cells were treated with 200 ng/ml interleukin 1-receptor antagonist (IL-1ra), 500 ng/ml soluble **TNF** receptor (sTNFr), or NaCl for 1 h. Isolated membrane proteins were used for Western blot analysis. Cell-associated and secreted IL-1β and **TNF**.alpha. protein content were determined in myocyte protein homogenates and cell culture supernatants by ELISA immunoblotting 3, 6, 24, 48 and 72 h after **treatment** with **LPS**. IL-1β (1.75-fold) and **TNF**.alpha. (1.62-fold) but not IL-6 and IFNγ induced RGS16 protein expression. **LPS** stimulated intracellular IL-1β expression within 6 h (847.1±172.9 pg/ 3x10(6) cells) followed by an increase in extracellular secretion up to 70.8±8.1 pg/3x10(6) cells after 48 h. In contrast, intracellular protein concentrations of **TNF**.alpha. were almost not detectable (0.03±0.01 pg/3x10(6) cells), but extracellular secretion was induced by **LPS** with a maximum at 6 h (653.9±36.3 pg/3x10(6) cells). The **LPS**-induced increase in RGS16 (1.6-fold) was blunted by IL-1ra but not by **TNF** α scavenging. Interestingly, both, the IL-1β- and **TNF** α-effect could be blocked by IL-1ra, indicating that also the **TNF**.alpha.-induced RGS16 expression is mediated by IL-1. We therefore conclude that **LPS** induces RGS16 protein expression by activation of the cytokine IL-1β in cardiac myocytes. Our data substantiate the role of IL-1β as an important mediator in **LPS**-induced cardiac failure.

L30 ANSWER 5 OF 23 BIOSIS on STN
2003:258367 Document No.: PREV200300258367. Cytokine upregulation in **heart failure** may not be a universal phenomenon. Lou,

Huiquan [Reprint Author]; Danelisen, Igor; Singal, Pawan K.. Physiology, Institute of Cardiovascular Sciences, 351 Tache Avenue, Winnipeg, Manitoba, R2H 2A6, Canada. louhuiq@hotmail.com; umdaneli@cc.umanitoba.ca; pawan_singal@sbrc.ca. FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 344.2. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. San Diego, CA, USA. April 11-15, 2003. FASEB.
ISSN: 0892-6638 (ISSN print). Language: English.

AB Background: **Heart failure** due to a variety of causes is generally accompanied by up-regulation of cytokines, such as **TNF**-(, IL-1(and IL-6. The current study investigated the expression of these cytokines in Adriamycin-induced cardiomyopathy and **heart failure** in rats. Methods: Both early and late-stage adriamycin-induced cardiomyopathy was produced in rats. Myocardial gene expression for cytokines, **TNF**-(, IL-1(and IL-6 was examined with DNA microarrays and RT-PCR. The protein levels of these cytokines in both plasma and myocardium were also studied by ELISA. Results and Conclusion: In the early stage, none of the three genes showed any up-regulation in both plasma and heart. During the late-stage **heart failure** was confirmed by clinical signs as well as homodynamic changes. In this stage, plasma **TNF**-(, IL-1(and IL-6 protein levels were not changed. However, myocardial **TNF**-(mRNA expression and protein levels were decreased, while both IL-1(mRNA and protein levels were not different compared to the control group. IL-6 mRNA expression was undetectable in both normal and ADR treated hearts. Positive control using lipopolysaccharides (**LPS**) **treatment** resulted in a significant increase in these three cytokines in the heart and plasma. DNA microarray analysis did not show gene expression both in control and adriamycin groups. These data suggest that **TNF**-(, IL-1(and IL-6 may not be involved in adriamycin-induced cardiomyopathy and **heart failure.**

L30 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
2002:888734 Document No. 137:384849 Preparation of 4-(4-pyridazinyl)pyrazole derivatives as p38MAP kinase (p38 mitogen-activated protein kinase) inhibitors. Minami, Nobuyoshi; Hasumi, Koichi; Ohta, Shuji; Sato, Shuichiro; Saito, Takahisa; Doi, Satoshi; Kobayashi, Motohiro; Sato, Jun; Asano, Hajime; Matsumoto, Yasuhiro (Teikoku Hormone Mfg. Co., Ltd., Japan). PCT Int. Appl. WO 2002092593 A1 20021121, 66 pp. DESIGNATED STATES: W: AU, CA, CN, JP, KR, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP4636 20020514. PRIORITY: JP 2001-146270 20010516.

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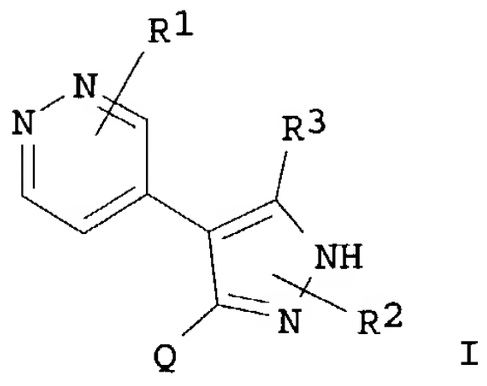

I

AB 4-(4-Pyridazinyl)pyrazole derivs. represented by the following general formula (I) or salts thereof [wherein Q = optionally substituted aryl or heteroaryl; R1 = H, halogeno, HO, lower alkoxy, NH2, aralkylamino, mono- or di(lower alkyl)amino, lower alkylthio; R2 = H, lower alkynyl, optionally hydroxy-substituted lower alkyl; R3 = H, lower alkyl, CH2CH(R4)-(A)n-Y, CH:C(R4)-(A)n-Y, CH2CH(R4)-(A)n-Y, NR4-CO-(A)n-Y, lower cycloalkyl (wherein A = lower alkylene; Y = (un)substituted aryl; R4 = H, lower alkyl; n = 0, 1)] are prepared These compds. have an excellent

inhibitory activity on p38 mitogen-activated protein kinase (p38MAPK), which is known to activate certain transcription factors such as **TNF**-κB, AP-1, and CREB binding to a DNA sequence common to tumor necrosis factor-α (**TNF**-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and cyclooxygenase II (COX-II) and thus promoting the transcription and production of proteins such as **TNF** -α, IL-1, IL-6, and COX-II from mRNA. Thereby they inhibit the production of **TNF**-α, IL-1, IL-6, and COX-II and are useful for preventing or treating diseases associated with **TNF**-α, IL-1, IL-6, and COX-II. The above diseases include chronic articular rheumatism, multiple sclerosis, osteoarthritis (arthrosis deformans), psoriasis, HIV, asthma, septic shock, inflammatory bowel diseases, Crohn's disease, Alzheimer's disease, diabetes, cachexia, osteoporosis, graft-vs.-host disease, adult respiratory distress syndrome, arteriosclerosis, gout, glomerulonephritis, congestive **heart failure**, ulcerative colitis, septicemia, cerebral malaria, restenosis, hepatitis, systemic lupus erythematosus, thrombosis, born resorption disease, chronic pulmonary inflammation disease, heart reperfusion disorder, kidney reperfusion disorder, cancer, writer's syndrome, imminent abortion, eczema, allograft rejection, or seizure. They also include fever, Behcet's disease, neuralgia, meningitis, sunburn, contact dermatitis, acute synovitis, spondylitis, muscle degeneration, neovascularization, conjunctivitis, psoriatic arthritis, viral myocarditis, pancreatitis, hemorrhage, arthritis, endotoxin shock, parasitic infection, tuberculosis, myocardial infarction, Hansen's disease, diabetic retinopathy, irritable bowel syndrome (IBS), transplant rejection, burn, bronchitis, ischemic heart disease, eclampsia, pneumonia, remission of swelling, backache (low back pain), pharyngolaryngitis (pharyngitis-laryngitis), Kawasaki disease (mucocutaneous lymphnode syndrome), spinal cord disease, or atopic dermatitis. Thus, 2.0 M LiN(CHMe2)2/heptane-THF-ethylbenzene was added dropwise to a solution of 3.83 g 4-methylpyridazine in 40 mL THF at -70° and stirred at room temperature, followed by adding a solution of 6.84 g Et 4-fluorobenzoate in 40 mL
THF at -70°, and the resulting mixture was stirred at room temperature for 3 h to give 40% 1-fluoro-4-(4-pyridazinylacetyl)benzene (II). To a solution of 4 g II in 80 mL THF was added 4.41 g N,N-dimethylformamide di-Me acetal and stirred at room temperature for 20 h, followed by distilling off the solvent
under reduced pressure, and the residue was dissolved in 60 mL ethanol, treated with 1.85 g hydrazine monohydrate, and stirred at 50° for 30 min to give 79% 3(5)-(4-fluorophenyl)-4-(4-pyridazinyl)pyrazole (III). In a p38MAP kinase-binding inhibitory assay, III in vitro showed IC50 of 6.5 nM for inhibiting the binding of a radioligand, [3H]-SB202190, i.e. 4-(4-fluorophenyl)-2-(4-hydroxy-3,4-di-3H-phenyl)-5-(4-pyridyl)imidazole, on cytosol of human monocyte THP-1 cell. III at 30 mg/kg in vivo inhibited the lipopolysaccharide (**LPS**)-induced production of **TNF**-α in mice by 84% after 6 h.

L30 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
2002:315096 Document No. 136:320419 Human IL-17-related protein LP-48 and therapeutic use thereof. Glasebrook, Andrew Lawrence; Liu, Ling; Newton, Christy Michelle; Tetreault, Jonathan Wendell (Eli Lilly and Company, USA). PCT Int. Appl. WO 2002033083 A2 20020425, 112 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US27737 20010928. PRIORITY: US 2000-PV240177 20001013; US 2001-PV309936 20010803.
AB The invention provides protein and cDNA sequences for a novel human

IL-17-related protein called LP-48 (also known as IL-17C and IL-21), which is a member of interleukin superfamily. The transgenic mice expressing LP-48 are used to test the function of LP-48 and possible therapeutic applications. LP-48 can protect the transgenic mice against **LPS** -induced septic shock and from **LPS**-induced death. LP-48 protein can inhibit **LPS**-induced increases in IFN-γ, IL-12, **TNF**-α and IL-6 secretion in transgenic mice. LP-48 can reduce apoptosis in human endothelial cells, more specifically, apoptosis induced by staurosporine. LP-48 can bind to the cell surface of endothelial cells and other tissues specifically through natural LP-48 receptors. Methods are provided for the **treatment** or prevention of atherosclerosis, allergic autoimmune diseases, endothelial cell apoptosis, allograft vasculopathy, hypertension, congestive **heart failure**, ischemia/reperfusion injury, type 1 diabetes, inflammation, immunodeficiencies, cancers, and infectious diseases by administering a human IL-17 related polypeptide and/or an antibody recognizing an epitope thereof to a patient in need of such therapy.

L30 ANSWER 8 OF 23 EMBASE
on STN

2002294975 EMBASE Effect of interleukin-10 on the production of tumor necrosis factor-alpha by peripheral blood mononuclear cells from patients with chronic **heart failure.** Bolger A.P.; Sharma R.; Von Haehling S.; Doehner W.; Oliver B.; Rauchhaus M.; Coats A.J.S.; Adcock I.M.; Anker S.D.. A.P. Bolger, Department of Clinical Cardiology, National Heart and Lung Institute, London SW3 6LY, United Kingdom. a.bolger@ic.ac.uk. American Journal of Cardiology 90/4 (384-389) 15 Aug 2002.

Refs: 29.

ISSN: 0002-9149. CODEN: AJCDAG.

Publisher Ident.: S 0002-9149(02)02494-3. Pub. Country: United States.

Language: English. Summary Language: English.

AB Chronic **heart failure** (HF) is a state of inflammatory immune activation characterized by elevated circulating levels of tumor necrosis factor-α (**TNF**-α). Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine that inhibits **TNF**-α production and lessens endotoxin bioactivity. It is not known whether IL-10 reduces lipopolysaccharide (**LPS**) stimulated **TNF** -α production of peripheral blood mononuclear cells (PBMCs) from patients with chronic HF. PBMCs were isolated from 15 patients with chronic HF (New York Heart Association functional class 3.0 ± 0.2, left ventricular ejection fraction 30 ± 2%, peak oxygen consumption 18.1 ± 0.8 ml/kg/min) and 15 healthy control subjects and stimulated with 1 and 10 ng/ml **LPS** for 24 hours with or without prior addition of IL-10 (10 ng/ml). **TNF**-α was quantified in cell-free supernatants by an enzyme-linked immunosorbent assay. **TNF** -α, soluble **TNF** receptors, IL-10, and **LPS** were quantified in plasma. **LPS** stimulated **TNF**-α production was highest in those patients in New York Heart Association class II ($p < 0.01$ vs New York Heart Association class III and IV, $p < 0.001$ vs control subjects). IL-10 reduced PBMC **TNF**-α production in all stimulated samples at 1 and 10 ng/ml **LPS** (mean reduction 43% at 1 ng/ml, $p < 0.01$ and 55% at 10 ng/ml, $p < 0.0001$). The percentage reduction in **TNF**-α release did not differ significantly between patients and control subjects or with respect to severity of chronic HF or baseline immune parameters. Independently of clinical severity, IL-10 profoundly inhibits **TNF**-α release from PBMCs isolated from patients with chronic HF. IL-10 is, therefore, a potential therapy for use in chronic HF associated with inflammatory immune activation.

L30 ANSWER 9 OF 23 MEDLINE on STN

2002652985. PubMed ID: 12411981. Preclinical and clinical assessment of the safety and potential efficacy of thalidomide in **heart failure.** Agoston Ildiko; Dibbs Ziad I; Wang Feng; Muller George;

Zeldis Jerome B; Mann Douglas L; Bozkurt Biykem. (Winters Center for Heart Failure Research, Cardiology Section, Department of Medicine, Veterans Affairs Medical Center, Baylor College of Medicine, Houston, Texas 77030, USA.) Journal of cardiac failure, (2002 Oct) 8 (5) 306-14. Journal code: 9442138. ISSN: 1071-9164. Pub. country: United States. Language: English.

AB BACKGROUND: Inflammatory mediators, especially tumor necrosis factor (**TNF**), have been implicated in **heart failure** (HF). Thalidomide has anti-inflammatory properties and selectively inhibits **TNF.** Thus far, thalidomide or thalidomide analogues have not been evaluated in patients with **heart failure** . METHODS: Thalidomide was assessed in preclinical and clinical studies. First, isolated cardiac myocytes were pretreated with thalidomide or thalidomide analogues, and **TNF** production was assessed after lipopolysaccharide (**LPS**) provocation. Second, to determine the safety and potential efficacy of thalidomide, an open-label dose escalation safety study was conducted in seven patients with advanced **heart failure.** RESULTS: Thalidomide and thalidomide analogues inhibited **LPS**-induced **TNF** biosynthesis in cardiac myocytes in a dose-dependent manner. Thalidomide analogues had a greater inhibitory effect on **TNF** production than did thalidomide. In patients with advanced HF, thalidomide was safe and potentially effective when used at lower doses. However, dose-limiting toxicity was observed in two patients. There was a significant increase in the 6-minute walk distance and a trend toward improvement in left ventricular ejection fraction and quality of life after 12 weeks of maintenance therapy with thalidomide. CONCLUSIONS: Taken together these results suggest that thalidomide or its derivatives may be useful in selected patients with HF. This potential needs to be studied in larger clinical trials.

L30 ANSWER 10 OF 23 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2001176141 EMBASE Effects of soluble **TNF** receptor **treatment** on lipopolysaccharide-induced myocardial cytokine expression. Kadokami T.; McTiernan C.F.; Kubota T.; Frye C.S.; Bounoutas G.S.; Robbins P.D.; Watkins S.C.; Feldman A.M.. A.M. Feldman, Cardiovasc. Inst. UPMC Hlth. Syst., 200 Lothrop S., S 572 Scaife Hall, Pittsburgh, PA 15213, United States. feldmanam@msx.upmc.edu. American Journal of Physiology - Heart and Circulatory Physiology 280/5 49-5 (H2281-H2291) 2001.
Refs: 60.
ISSN: 0363-6135. CODEN: AJPPDI. Pub. Country: United States. Language: English. Summary Language: English.

AB Tumor necrosis factor (**TNF**)-α plays a key role in the pathogenesis of septic shock syndrome, and myocardial **TNF** -α expression may contribute to this pathophysiology. We examined the myocardial expression of **TNF**-α-related cytokines and chemokines in mice exposed to lipopolysaccharide (**LPS**) and tested the effects of anti-**TNF** therapy on myocardial cytokine expression. Cytokine mRNA levels were measured by RNase protection assay, and protein levels in the plasma and myocardium were assessed by enzyme-linked immunosorbent assays. **LPS** (4 μg/g body wt ip) induced marked cytokine expression, including **TNF**-α, interleukin (IL)-1β, IL-6, and monocyte chemotactic protein (MCP)-1, in both the plasma and myocardium. Pretreatment with adenovirus-mediated **TNF** receptor fusion protein (AdTNFR1; 10(9) plaque-forming units iv) decreased plasma cytokine levels. In contrast, whereas myocardial IL-1β expression was also suppressed, expression of IL-6 and MCP-1 was not inhibited by AdTNFR1. In summary, anti-**TNF** **treatment** differentially altered the cytokine expression in the plasma and myocardium during endotoxemia. Inability to block myocardial expression of IL-6 and MCP-1 suggests a possible mechanism for the failure of anti-**TNF** therapies in the **treatment** of endotoxin shock.

L30 ANSWER 11 OF 23 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2001:242294 The Genuine Article (R) Number: 409BT. Ace-inhibition with quinapril modulates the nitric oxide pathway in normotensive rats. Bachetti T; Comini L; Pasini E; Cargnoni A; Curello S; Ferrari R (Reprint) . Univ Ferrara, Osped S Anna, Nuove Clin, Corso Giovecca 203, I-44100 Ferrara, Italy (Reprint); Univ Ferrara, Chair Cardiol, I-44100 Ferrara, Italy; Spedali Civili, Div Cardiol, I-25125 Brescia, Italy; IRCCS, Cardiovasc Pathophysiol Res Ctr, Salvatore Maugeri Fdn, Gussago, Italy. JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY (MAR 2001) Vol. 33, No. 3, pp. 395-403. Publisher: ACADEMIC PRESS LTD. 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND. ISSN: 0022-2828. Pub. country: Italy. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Angiotensin-converting enzyme (ACE) inhibitors exert some cardiovascular benefits by improving endothelial function. We evaluated the effects of chronic **treatment** with quinapril (Q) on the (L)-arginine/nitric oxide (NO) pathway in normotensive rats under baseline and inflammatory conditions. The role of bradykinin was also investigated. The animals received for 1 week either the ACE-inhibitor Q (1 and 10 mg/kg/day). the B-2, receptor antagonist HOE 140, Q + HOE 140, or no drug. At the end of chronic **treatment**, rats underwent either a 6-h placebo or an E. coli endotoxin challenge. The following measurements were made: (i) endothelial and inducible NO synthase (eNOS and iNOS) protein expression: (ii) eNOS/iNOS activity; (iii) serum levels of nitrite/ nitrate and tumour necrosis factor (**TNF**)-alpha; (iv) NO in the expired air (eNO). Q increased baseline aortic eNOS protein expression (up to 99%, P<0.001) and activity ((L)-citrulline synthesis up to 94%. P<0.01; serum nitrite/ nitrate up to 55%, P<0.05). HOE 140 partially reversed Q-induced upregulation of eNOS (P<0.05). Moreover, Q counteracted **LPS** effects, i.e. increased the impaired eNOS pathway and limited iNOS induction (up to 94 and 24%, respectively), and reduced the increased nitrite/nitrate and **TNF**-alpha serum levels as well as eNO (up to 25, 38 and 28%, respectively. P<0.01 for all comparisons). HOE 140 did not influence Q effects on iNOS during endotoxaemia. In conclusion, in (patho)physiological conditions in rats, Q up-regulated eNOS with a bradykinin-mediated mechanism. while downregulated iNOS with a possible **TNF**-<alpha>-mediated mechanism. (C) 2001 Academic Press.

L30 ANSWER 12 OF 23 MEDLINE on STN
2001223234. PubMed ID: 11192310. Comparison of tumor necrosis factor-alpha effect on the expression of iNOS in macrophage and cardiac myocytes. Sanders D B; Larson D F; Hunter K; Gorman M; Yang B. (Circulatory Sciences Graduate Perfusion Program, Sarver Heart Center, University of Arizona, Tucson 85724, USA.) Perfusion, (2001 Jan) 16 (1) 67-74. Journal code: 8700166. ISSN: 0267-6591. Pub. country: England: United Kingdom. Language: English.

AB Proinflammatory cytokines, including tumor necrosis factor-alpha (**TNF**-alpha), are elevated during cardiopulmonary bypass (CPB), **heart failure**, and inflammatory cardiac and systemic diseases. Elevated **TNF**-alpha has been linked to diminished cardiac function, decreased systemic vascular resistance, as well as renal and pulmonary dysfunction. It is understood that myocardial tissues can express **TNF**-alpha, which results in the induction of inducible nitric oxide synthase (iNOS) leading to a significant decline in cardiac function and other direct effects. The hypothesis of this study was to determine if **TNF**-alpha would stimulate iNOS and its product nitric oxide (NO) similarly in immortalized macrophage and cardiac myocytes. Cultured macrophages (RAW 264.7) and cardiac myocytes (HL-1) were placed into two **treatment** groups and a control. The **treatments** included: (1) **TNF**-alpha and lipopolysaccharide (**LPS**); and (2) **LPS**, **TNF** -alpha, interleukin-1beta (IL-1beta) and interferon-gamma (IFN-gamma) incubated for 8 h. The macrophage expression of iNOS increased by 365% ($p < 0.01$) and its product, NO, increased proportionally. The expression of iNOS in the cardiac myocyte did not increase with **TNF**-alpha and **LPS**. However, with the addition of IFN-alpha and IL-1beta iNOS increased to 140% of control ($p < 0.05$). Myocyte cGMP and NO did not

increase significantly with **TNF**-alpha **treatment.** This study suggests that HL-1 myocyte iNOS cannot be induced by **TNF** -alpha, unlike macrophage iNOS. Furthermore, the resultant cardiac dysfunction, secondary to proinflammatory cytokines effects, is regulated via diverse pathways.

L30 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
2000:608753 Document No. 133:193275 Preparation of phosphoric acid derivatives as **TNF**-α production inhibitors. Matsui, Toshiaki; Ohmawari, Nagashige (Ono Pharmaceutical Co., Ltd., Japan). PCT Int. Appl. WO 2000050429 A1 20000831, 253 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP1005 20000222. PRIORITY: JP 1999-44840 19990223; JP 1999-283104 19991004.

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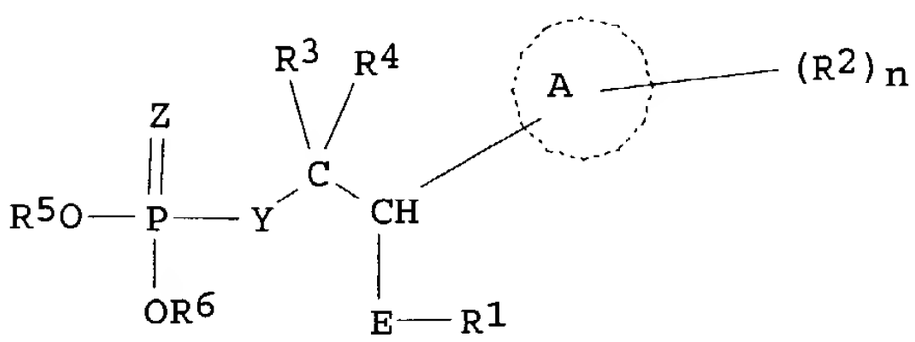

I

AB The title compds. I [R1 = alkyl, etc.; ring A = heterocyclic ring, etc.; R2 = NR7CO, etc.; R7 = H, alkyl; R3, R4 = H, alkyl, etc.; further details on R3 and R4 are given; n = 0 or n ≥ 1; R5, R6 = H, alkyl, Ph, etc.; E = NR7CO, etc.; Y, Z = O, S; provisos are given] are prepared I are useful as preventives and/or remedies for rheumatoid arthritis, ulcerative colitis, Crohn's disease, hepatitis, sepsis, hemorrhagic shock, multiple sclerosis, brain infarction, diabetes, interstitial pneumonia, uveitis, pain, glomerulonephritis, HIV-associated diseases, cachexia, myocardial infarction, chronic **heart failure**, Hansen's disease, infection, etc. (2R)-2-Phenyl-2-(N-octanoylamino)ethyl phosphate disodium salt showed ED50 of 2.6 mg/kg against **TNF**-α production in mice treated with **LPS.** A formulation is given.

L30 ANSWER 14 OF 23 MEDLINE on STN
2001012623. PubMed ID: 11009565. Peroxisome proliferator-activated receptor activators inhibit lipopolysaccharide-induced tumor necrosis factor-alpha expression in neonatal rat cardiac myocytes. Takano H; Nagai T; Asakawa M; Toyozaki T; Oka T; Komuro I; Saito T; Masuda Y. (Third Department of Internal Medicine, Chiba University School of Medicine, Japan.. htakano-cib@umin.ac.jp) . Circulation research, (2000 Sep 29) 87 (7) 596-602. Journal code: 0047103. ISSN: 1524-4571. Pub. country: United States. Language: English.

AB Peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to the nuclear receptor superfamily. Recently, PPAR activators have been shown to inhibit the production of proinflammatory cytokines in macrophages or vascular smooth muscle cells. It has been reported that tumor necrosis factor-alpha (**TNF**-alpha) expression is elevated in the failing heart and that **TNF**-alpha has a negative inotropic effect on cardiac myocytes. Therefore, we examined the effects of PPARalpha and PPARgamma activators on expression of **TNF** -alpha in neonatal rat cardiac myocytes. Northern blot analysis revealed

expression of PPARalpha and PPARgamma mRNA in cardiac myocytes. Immunofluorescent staining demonstrated that both PPARalpha and PPARgamma were expressed in the nuclei of cells. When cardiac myocytes were transfected with PPAR responsive element (PPRE)-luciferase reporter plasmid, both PPARalpha and PPARgamma activators increased the promoter activity. Cardiomyocytes were stimulated with lipopolysaccharide (**LPS**), and the levels of **TNF**-alpha in the medium were measured by ELISA. After exposure to **LPS**, the levels of **TNF**-alpha significantly increased. However, pretreatment of myocytes with PPARalpha or PPARgamma activators decreased **LPS** -induced expression of **TNF**-alpha in the medium. Both PPARalpha and PPARgamma activators also inhibited **LPS**-induced increase in **TNF**-alpha mRNA in myocytes. In addition, electrophoretic mobility shift assays demonstrated that PPAR activators reduced **LPS** -induced nuclear factor-kappaB activation. These results suggest that both PPARalpha and PPARgamma activators inhibit cardiac expression of **TNF**-alpha in part by antagonizing nuclear factor-kappaB activity and that **treatment** with PPAR activators may lead to improvement in congestive **heart failure.**

L30 ANSWER 15 OF 23 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:773558 The Genuine Article (R) Number: 362AB. Peroxisome proliferator-activated receptor activators inhibit lipopolysaccharide-induced turner necrosis factor-alpha expression in neonatal rat cardiac myocytes. Takano H (Reprint); Nagai T; Asakawa M; Toyozaki T; Oka T; Komuro I; Saito T; Masuda Y. CHIBA UNIV, SCH MED, DEPT INTERNAL MED 3, CHUO KU, 1-8-1 INOHANA, CHIBA 2608670, JAPAN (Reprint); UNIV TOKYO, GRAD SCH MED, DEPT CARDIOVASC MED, TOKYO, JAPAN. CIRCULATION RESEARCH (29 SEP 2000) Vol. 87, No. 7, pp. 596-602. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621. ISSN: 0009-7330. Pub. country: JAPAN. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to the nuclear receptor superfamily. Recently, PPAR activators have been shown to inhibit the production of proinflammatory cytokines in macrophages or vascular smooth muscle cells. It has been reported that tumor necrosis factor-alpha (**TNF**-alpha) expression is elevated in the failing heart and that **TNF**-alpha has a negative inotropic effect on cardiac myocytes. Therefore, we examined the effects of PPAR alpha and PPAR gamma activators on expression of **TNF**-alpha in neonatal rat cardiac myocytes. Northern blot analysis revealed expression of PPAR alpha and PPAR gamma mRNA in cardiac myocytes. Immunofluorescent staining demonstrated that both PPAR alpha and PPAR gamma were expressed in the nuclei of cells. When cardiac myocytes were transfected with PPAR responsive element (PPRE)-luciferase reporter plasmid, both PPAR alpha and PPAR gamma activators increased the promoter activity. Cardiomyocytes were stimulated with Lipopolysaccharide (**LPS**), and the levels of **TNF**-alpha in the medium were measured by ELISA. After exposure to **LPS**, the levels of **TNF**-alpha significantly increased. However, pretreatment of myocytes with PPAR alpha or PPAR gamma activators decreased **LPS** -induced expression of **TNF**-alpha in the medium. Both PPAR alpha and PPAR gamma activators also inhibited **LPS**-induced increase in **TNF**-alpha mRNA in myocytes. In addition, electrophoretic mobility shift assays demonstrated that PPAR activators reduced **LPS** -induced nuclear factor-kappa B activation. These results suggest that both PPAR alpha and PPAR gamma activators inhibit cardiac expression of **TNF**-alpha in part by antagonizing nuclear factor-kappa B activity and that **treatment** with PPAR activators may lead to improvement in congestive **heart failure.**

L30 ANSWER 16 OF 23 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:503396 The Genuine Article (R) Number: 209PY. The effect of vesnarinone on **TNF** alpha production in human peripheral blood mononuclear cells and microglia: a preclinical study for the **treatment** of

multiple sclerosis. Jiang H; Bielekova B; Okazaki H; ClarenceSmith K; Johnson K P; Bergey G; Martin R; DhibJalbut S (Reprint). UNIV MARYLAND HOSP, DEPT NEUROL, ROOM N4W46, 22 S GREENE ST, BALTIMORE, MD 21201 (Reprint); UNIV MARYLAND, DEPT NEUROL, BALTIMORE, MD 21201; NINCDS, NEUROIMMUNOL BRANCH, BETHESDA, MD 20842; OTSUKA PHARMACEUT CO LTD, TOKUSHIMA 7710192, JAPAN. JOURNAL OF NEUROIMMUNOLOGY (1 JUN 1999) Vol. 97, No. 1-2, pp. 134-145. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0165-5728. Pub. country: USA; JAPAN. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Vesnarinone (OPC-8212) is a synthetic quinolinone derivative with inotropic and immunomodulatory effects. Vesnarinone has been shown to inhibit tumor necrosis factor-alpha (**TNF** alpha) produced by mitogen stimulated macrophages. and to inhibit phosphodiesterase (PDE) type III in cardiac muscle. **TNF** alpha and interferon-gamma (IFN gamma) have been implicated in the pathogenesis of autoimmune diseases, and both cytokines are targets for therapeutic intervention. IFN gamma can enhance autoimmune disease through direct effects, and indirectly by priming macrophages to produce **TNF** alpha. In this study, we demonstrate that while vesnarinone enhances basal **TNF** alpha levels, it inhibits **TNF** alpha production in peripheral blood mononuclear cells from multiple sclerosis (MS) patients and healthy donors stimulated with lipopolysaccharide (**LPS**) or primed with IFN gamma and stimulated with suboptimal doses of **LPS**. In addition, vesnarinone inhibited **TNF** alpha production in primary adult human microglial cultures. However, in contrast to rolipram, another **TNF** alpha inhibiting agent, vesnarinone failed to inhibit **TNF** alpha production by myelin basic protein specific T-cell lines. As oral **TNF** inhibitors are currently being considered in the USA for clinical application in MS, the implications of our findings on the development of vesnruinone for **treatment** of hlS are discussed.

L30 ANSWER 17 OF 23 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:65114 The Genuine Article (R) Number: 155LC. **LPS**-Induced **TNF**-alpha release from and apoptosis in rat cardiomyocytes: Obligatory role for CD14 in mediating the **LPS** response.
Comstock K L; Krown K A (Reprint); Page M T; Martin D; Ho P; Pedraza M; Castro E N; Nakajima N; Glembotski C C; Quintana P J E; Sabbadini R A. REES STEALY RES FDN, 2001 4TH AVE, SAN DIEGO, CA 92101 (Reprint); REES STEALY RES FDN, SAN DIEGO, CA 92101; SAN DIEGO STATE UNIV, DEPT BIOL, SAN DIEGO, CA 92182; SAN DIEGO STATE UNIV, GRAD SCH PUBL HLTH, SAN DIEGO, CA 92182. JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY (DEC 1998) Vol. 30, No. 12, pp. 2761-2775. Publisher: ACADEMIC PRESS LTD. 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND. ISSN: 0022-2828. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The bacterial endotoxin lipopolysaccharide (**LPS**) contributes to the cardiovascular collapse and death observed in patients with sepsis. Because **LPS** has such profound effects on cardiac performance, we speculate that direct effects of **LPS** could be demonstrated on cardiomyocytes in culture, and that these direct effects are mediated by the **LPS** receptor, CD14. Accordingly, in this study, we provide evidence for CD14-dependent cardiotoxic effects of **LPS** including the **LPS**-stimulated secretion of tumor necrosis factor alpha (**TNF**-alpha) from cardiomyocytes. **TNF**-alpha is an inflammatory cytokine which is renown for its negative inotropic effects on cardiac performance, but has not until recently been shown to be produced by cardiac cells. In this study, **LPS** was found to stimulate strongly in a dose-dependent manner the secretion of **TNF** -alpha from cultured adult rat cardiomyocytes. Further, **LPS** -induced **TNF**-alpha secretion was blocked by an inhibitor of **TNF**-alpha processing metallomatrix protease inhibitor (TAPI). Molecular and immulogical evidence demonstrated the presence of **LPS** receptors (CD14) on cardiomyocytes. Attenuated **TNF**

-alpha secretion following PI-PLC **treatment** confirmed the functional importance of CD14 for **LPS**-mediated myocardial effects. Importantly, **LPS** also triggered apoptosis in cultured cardiomyocytes as quantified by single-cell gel electrophoresis of nuclei exhibiting DNA fragmentation patterns characteristic of apoptosis (i.e. cardiac comets). Apoptotic cell death was blocked by pre-incubation with the soluble **TNF**-alpha receptor fragment (TNFRII:Fc), suggesting that **LPS**-induced apoptosis was **TNF**-alpha-dependent and probably involved an autocrine function for the **TNF**-alpha whose secretion was under **LPS** control. The results of this study suggest that the cardiodepressant effects of **LPS** are dependent on CD14 signaling and may not only be due to acute negative inotropic effects of TNE-alpha but also may be complicated by **TNF** -alpha-induced apoptotic cell death which effectively reduces the number of working myocardial cells. (C) 1998 Academic Press.

L30 ANSWER 18 OF 23 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

1998286391 EMBASE **TNF**-α and myocardial depression in endotoxemic rats: Temporal discordance of an obligatory relationship. Meng X.; Ao L.; Meldrum D.R.; Cain B.S.; Shames B.D.; Selzman C.H.; Banerjee A.; Harken A.H.. X. Meng, Dept. of Surgery, Box C-320, Univ. of Colorado Health Sci. Ctr., 4200 East 9th Ave., Denver, CO 80262, United States. American Journal of Physiology - Regulatory Integrative and Comparative Physiology 275/2 44-2 (R502-R508) 1998.
Refs: 40.
ISSN: 0363-6119. CODEN: AJPRDO. Pub. Country: United States. Language: English. Summary Language: English.

AB Exogenous tumor necrosis factor-α (**TNF**-α) induces delayed myocardial depression in vivo but promotes rapid myocardial depression in vitro. The temporal relationship between endogenous **TNF**-α and endotoxemic myocardial depression is unclear, and the role of **TNF**-α in this myocardial disorder remains controversial. Using a rat model of endotoxemia not complicated by shock, we sought to determine 1) the temporal relationship of changes in circulating and myocardial **TNF**-α with myocardial depression, 2) the influences of protein synthesis inhibition or immunosuppression on **TNF**-α production and myocardial depression, and 3) the influence of neutralization of **TNF** -α on myocardial depression. Rats were treated with lipopolysaccharide (**LPS**, 0.5 mg/kg ip). Circulating and myocardial **TNF**-α increased at 1 and 2 h, whereas myocardial contractility was depressed at 4 and 6 h. Pretreatment with cycloheximide or dexamethasone abolished the increase in circulating and myocardial **TNF**-α and preserved myocardial contractile function. Similarly, **treatment** with **TNF** binding protein immediately after **LPS** prevented myocardial depression. We conclude that endogenous **TNF**-α mediates delayed myocardial depression in endotoxemic rats and that inhibition of **TNF**-α production or neutralization of **TNF**-α preserves myocardial contractile function in endotoxemia.

L30 ANSWER 19 OF 23 MEDLINE on STN

97459578. PubMed ID: 9315538. Modulation of cytokine production and protection against lethal endotoxemia by the cardiac glycoside ouabain. Matsumori A; Ono K; Nishio R; Igata H; Shioi T; Matsui S; Furukawa Y; Iwasaki A; Nose Y; Sasayama S. (Department of Cardiovascular Medicine, Kyoto University, Japan.. amat@kuhp.kyoto-u.ac.jp) . Circulation, (1997 Sep 2) 96 (5) 1501-6. Journal code: 0147763. ISSN: 0009-7322. Pub. country: United States. Language: English.

AB BACKGROUND: Recent studies have shown that cytokines are capable of modulating cardiovascular function and that some drugs used in the **treatment** of **heart failure** variably modulate the production of cytokines. To examine whether cardiac glycosides also modulate cytokine production, we evaluated the effects of ouabain on the

production of cytokines in vitro and in vivo. METHODS AND RESULTS: Human peripheral blood mononuclear cells (PBMC) were obtained from healthy volunteers. PBMC were cultured with or without ouabain in the presence or absence of lipopolysaccharide (**LPS**). Ouabain induced the production of interleukin (IL)-1beta, IL-6, and tumor necrosis factor (**TNF**)-alpha in PBMC and induced mRNA of these cytokines, an induction apparently at the transcriptional level. Amiloride, staurosporin, and genistein inhibited cytokine production, and protein kinase C and tyrosine kinase appeared to be involved in the modulation of cytokine production induced by ouabain. However, when PBMC were stimulated with **LPS**, ouabain suppressed the production of IL-6 and **TNF**-alpha. To investigate whether ouabain modulates cytokine production in vivo, we evaluated the effects of ouabain in **LPS**-treated mice. Ouabain was found to protect against **LPS**-induced lethal toxicity in mice and decreased circulating IL-6 and **TNF**-alpha levels in vivo. CONCLUSIONS: These previously unrecognized immunomodulating effects of a cardiac glycoside may explain either the beneficial or the detrimental effects of these drugs in **heart failure** patients.

L30 ANSWER 20 OF 23 MEDLINE on STN

97177413. PubMed ID: 9024938. Vesnarinone is a selective inhibitor of macrophage **TNF**(alpha) release. Kambayashi T; Mazurek N; Jacob C O; Wei N; Fong M; Strassmann G. (Department of Immunology, Otsuka-America Pharmaceutical Inc., Rockville, MD 20850, USA.) International journal of immunopharmacology, (1996 Jun-Jul) 18 (6-7) 371-8. Journal code: 7904799. ISSN: 0192-0561. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Vesnarinone is an experimental drug that has been used successfully in the **treatment** of congestive **heart failure** patients. In this report we investigate the effect of vesnarinone on the cytokine secretory products of mononuclear phagocytes. In a concentration-dependent manner, the drug inhibits the endotoxin(**LPS**)-stimulated release of tumor necrosis factor (**TNF**) alpha and suppresses interleukin(IL)-6 release, but does not affect the release of IL-1 alpha, IL-10 and leukemia inhibitory factor (LIF) by mouse peritoneal macrophages. Using competitive polymerase chain reaction (PCR) analyses, we find that vesnarinone significantly reduces **TNF** (alpha), but not IL-10 mRNA. In addition to **LPS**, the drug inhibits **TNF**(alpha) release induced by several other stimuli. The inhibitory effect of the drug on the **TNF**(alpha) biosynthesis can be observed in differentiated human monocytes, in macrophage cell lines, and in synovial adherent cells from rheumatoid arthritis patients. Although the precise mode of action of vesnarinone in the signal transduction pathway leading to the selective inhibition of **TNF** (alpha) is not known, the drug might be useful in the **treatment** of diseases involving that cytokine.

L30 ANSWER 21 OF 23 MEDLINE on STN

95057852. PubMed ID: 7968253. Vesnarinone prolongs survival and reduces lethality in a murine model of lethal endotoxemia. Matsui S; Matsumori A; Sasayama S. (Department of Internal Medicine, Kyoto University Hospital, Japan.) Life sciences, (1994) 55 (22) 1735-41. Journal code: 0375521. ISSN: 0024-3205. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Vesnarinone (3,4-Dihydro-6-[4(3,4-dimethoxybenzoyl)-1-piperanizyl]-2(1H)-quino linone), a recently synthesized quinolinone derivative with positive inotropic properties, has been reported the survival of patients with chronic congestive **heart failure.** However, the mechanisms that contribute to this improvement are not yet well understood. There is increasing evidence that vesnarinone has novel immunosuppressive properties related to its inhibition of cytokine production. Cytokines have been shown to play a pivotal role in the pathophysiologic consequences of fatal bacteremic shock. In this study, we investigated the effects of vesnarinone in a murine model of lethal endotoxemia induced by lipopolysaccharide (**LPS**). Eight-week-old female BALB/c mice were given 300 or 400 micrograms of **LPS**, and

50 or 100 mg/kg of vesnarinone was administered by oral gavage and/or 10 or 30 micrograms of vesnarinone was given intra peritoneally. Vesnarinone prolonged the median survival time and reduced lethality when given at the same time as the **LPS** injection. However, vesnarinone did not have a beneficial effect when administered 2 hours after **LPS treatment.** Plasma **TNF**-alpha reached a maximum level 1 hour after **LPS** challenge, and vesnarinone reduced the plasma level of **TNF**-alpha, when administered at the same time as **LPS** injection. Vesnarinone had protective effects against lethal endotoxemia; these effects were considered to be due to the suppression of **TNF**-alpha production. These findings suggest that vesnarinone may be a promising agent for the **treatment** of bacterial sepsis and shock.

L30 ANSWER 22 OF 23 MEDLINE on STN

94170507. PubMed ID: 8124835. Vesnarinone, a new inotropic agent, inhibits cytokine production by stimulated human blood from patients with **heart failure.** Matsumori A; Shioi T; Yamada T; Matsui S; Sasayama S. (Department of Internal Medicine, Faculty of Medicine, Kyoto University, Japan.) Circulation, (1994 Mar) 89 (3) 955-8. Journal code: 0147763. ISSN: 0009-7322. Pub. country: United States. Language: English.

AB BACKGROUND: Vesnarinone, a quinolinone derivative, is a recently synthesized positive inotropic agent that has been shown to dramatically improve the survival of patients with **heart failure.** However, the mechanism of action of vesnarinone remains unknown. Reversible neutropenia complicated with vesnarinone therapy suggests that vesnarinone may modulate the production of cytokines. Because tumor necrosis factor (**TNF**)-alpha and other cytokines have been shown to depress myocardial contractility, we investigated the effects of vesnarinone on the production of various cytokines. METHODS AND RESULTS: We studied the effects of vesnarinone on cytokine production by lipopolysaccharide (**LPS**)-stimulated whole blood from seven patients with **heart failure** and from five healthy volunteers. Heparinized blood was diluted in RPMI and stimulated with **LPS.** Vesnarinone was added in a range of 1 to 30 micrograms/mL, the blood was incubated for 24 hours, and interleukin (IL)-1 alpha, IL-1 beta, IL-6, **TNF**-alpha, interferon (IFN)-gamma, and granulocyte colony-stimulating factor (G-CSF) were measured by an enzyme-linked immunosorbent assay. **LPS** stimulation induced a more prominent increase in **TNF**-alpha in patients with **heart failure** than in healthy volunteers. Vesnarinone inhibited the production of **TNF**-alpha and IFN-gamma both in healthy volunteers and in patients with **heart failure.** IL-1 alpha and IL-1 beta were also suppressed in healthy volunteers, but this response was variable, and a significant reduction was not seen in patients with **heart failure.** Marked inhibition of G-CSF and other cytokines by vesnarinone was observed in one patient who had developed neutropenia as a result of vesnarinone therapy. CONCLUSIONS: Although the number of study patients was small and the results are preliminary, these findings provide evidence that vesnarinone plays an important role in the regulation of cytokines and suggest that the reduction of cytokine release may contribute to the beneficial effects of the drug in the **treatment** of **heart failure.** Furthermore, the measurement of cytokines may be useful in predicting the occurrence of neutropenia, which has been occasionally reported in patients treated with vesnarinone.

L30 ANSWER 23 OF 23 MEDLINE on STN

94029956. PubMed ID: 8216257. Vesnarinone inhibits production of HIV-1 in cultured cells. Maruyama I; Maruyama Y; Nakajima T; Kitajima I; Osame M; Zhao J Q; Chen I S; Nakai S; Ikeda M; Yabu-uchi Y; +. (Department of Clinical Medicine, School of Medicine, Kagoshima University, Japan.) Biochemical and biophysical research communications, (1993 Sep 30) 195 (3) 1264-71. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Vesnarinone, a synthetic oral cardiotonic agent that has been used for **treatment** of patients with congestive **heart failure**, was found to inhibit replication of HIV-1 in a peripheral blood lymphocytes model and in chronically infected macrophages at clinically achieved concentrations. Vesnarinone has no direct inhibitory activity against the reverse transcriptase of HIV-1, syncytium formation in short term assays, or retroviral protease. In addition, vesnarinone inhibits production of **TNF**-alpha and IL-6 by human peripheral blood mononucleated cells stimulated with **LPS**. These observations suggest that vesnarinone may be therapeutically useful in patients infected with HIV-1.

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